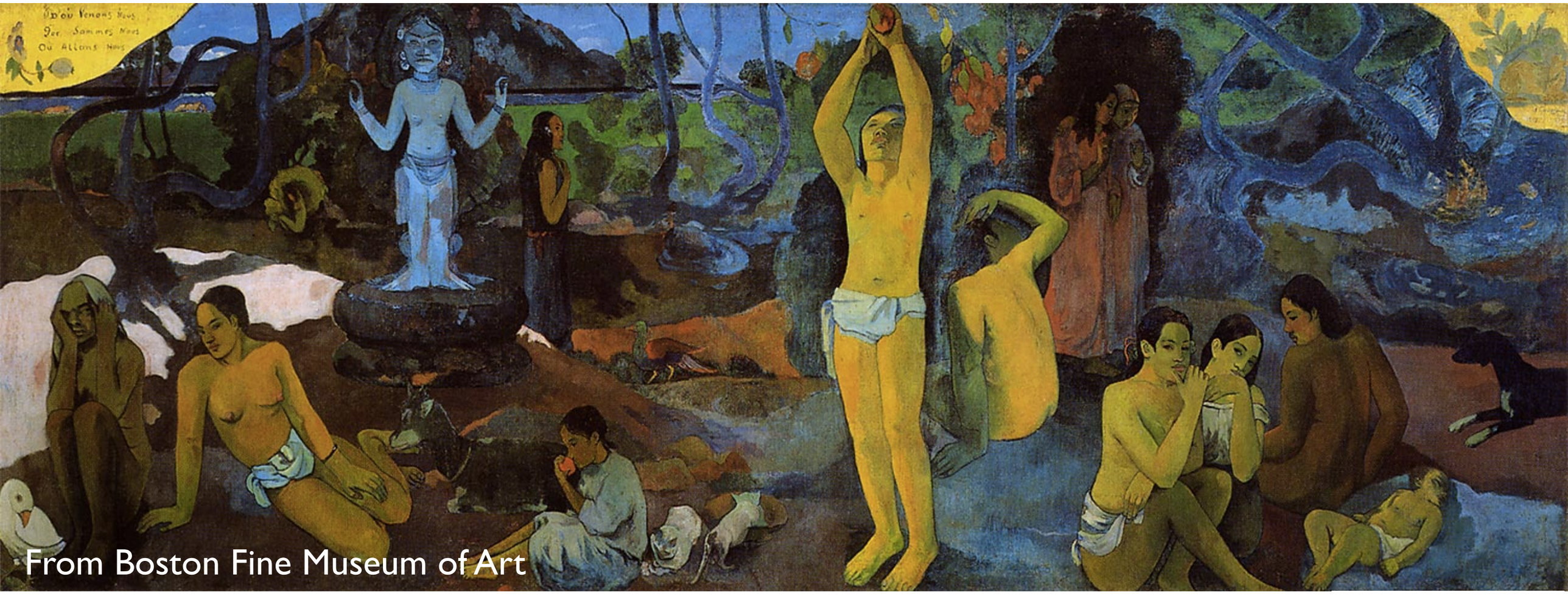
Molecular mechanisms for corticogenesis

Class for Graduate School of Life Sciences 190418

Molecular mechanisms for corticogenesis



From Boston Fine Museum of Art

Tohoku University Graduate School of Medicine
Department of Developmental Neuroscience
Noriko Osumi

NEURO GLOBAL
Tohoku University

「個性」創発脳

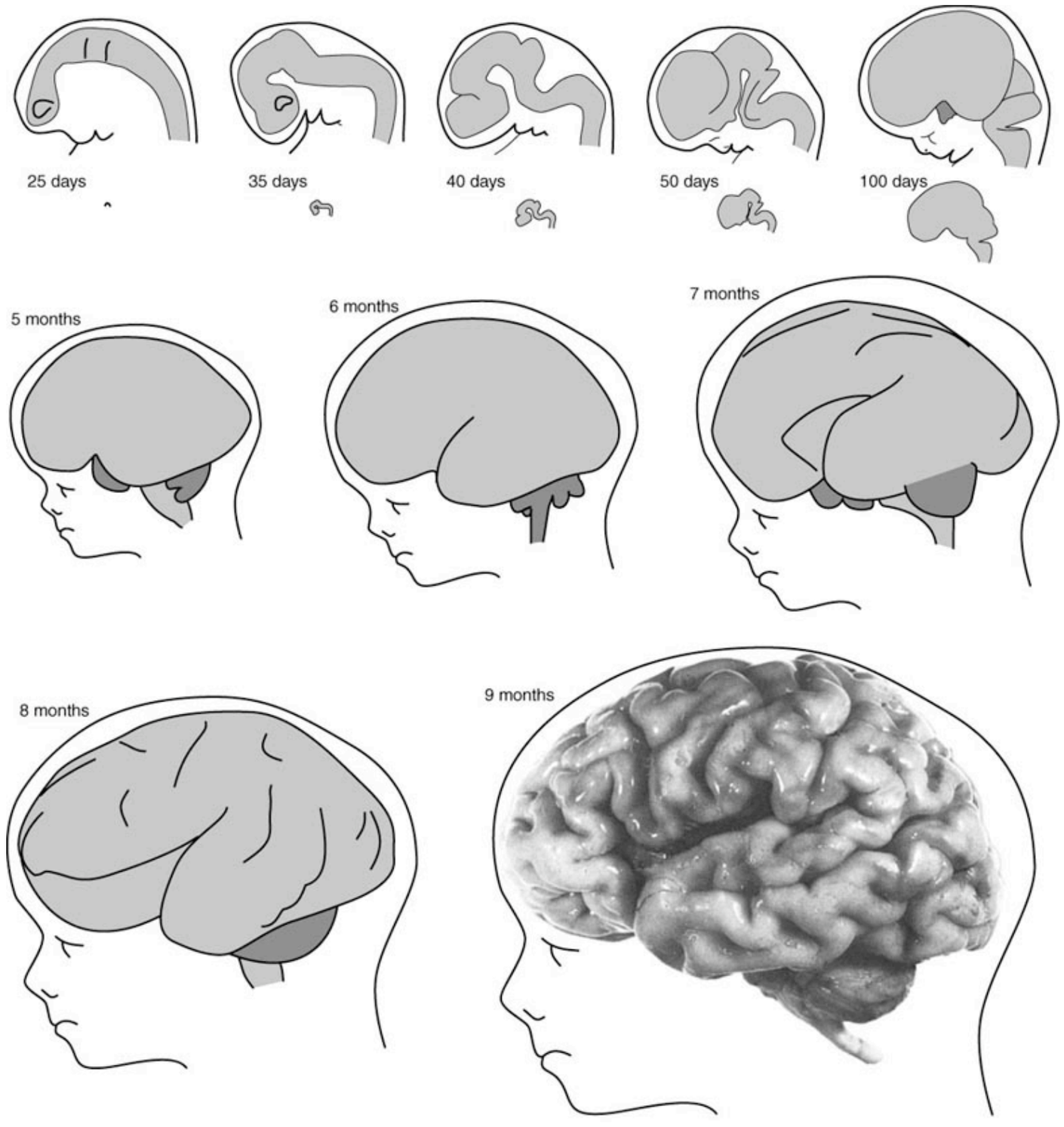
No handout

- Lecture materials will later be uploaded on TOUR (Tohoku University Repository)

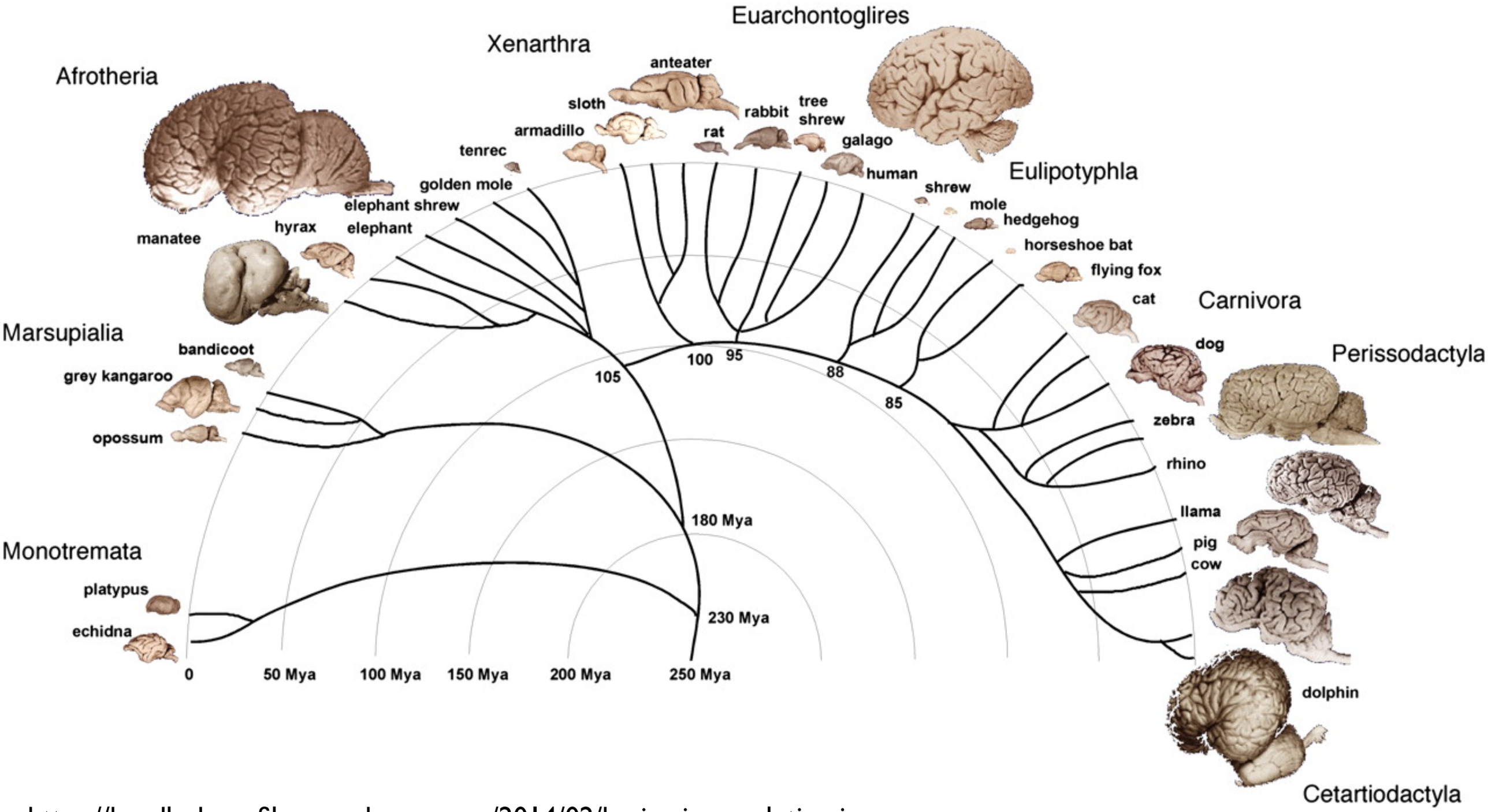
For students:

- How to ask a unique/important question
- How to solve the question

How the brain is developed?



How diverse brains are evolved?



https://handleshaus.files.wordpress.com/2014/02/brain-size-evolution.jpg

Four areas of biology by Tinbergen

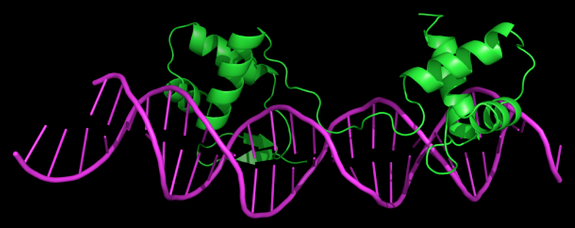
FOUR AREAS OF BIOLOGY: FOUR QUESTIONS		Two objects of explanation	
		Developmental/historical A sequence that results in the trait	**Single form** The trait at one slice in time
Two kinds of explanations	**Proximate** Explains how organisms work by describing their mechanisms and their ontogeny	**Ontogeny** **Q: How does the trait develop in individuals?** A: Description of the trait's forms at sequential life stages, and the mechanisms that control development.	**Neurophysiology**
	Evolutionary Explains how a species came to its current form by describing a sequence of forms, and how they were influenced by selection and other evolutionary factors.	**Phylogeny** **Q: What is the phylogenetic history of the trait?** **A:** Description of the history of the trait as reconstructed from its phenotype and genotype precursors	**Adaptive significance** **Q: How have variations in the trait interacted with environments to influence fitness in ways that help to explain the trait's form?** A: Description of how variations in the trait have influenced fitness

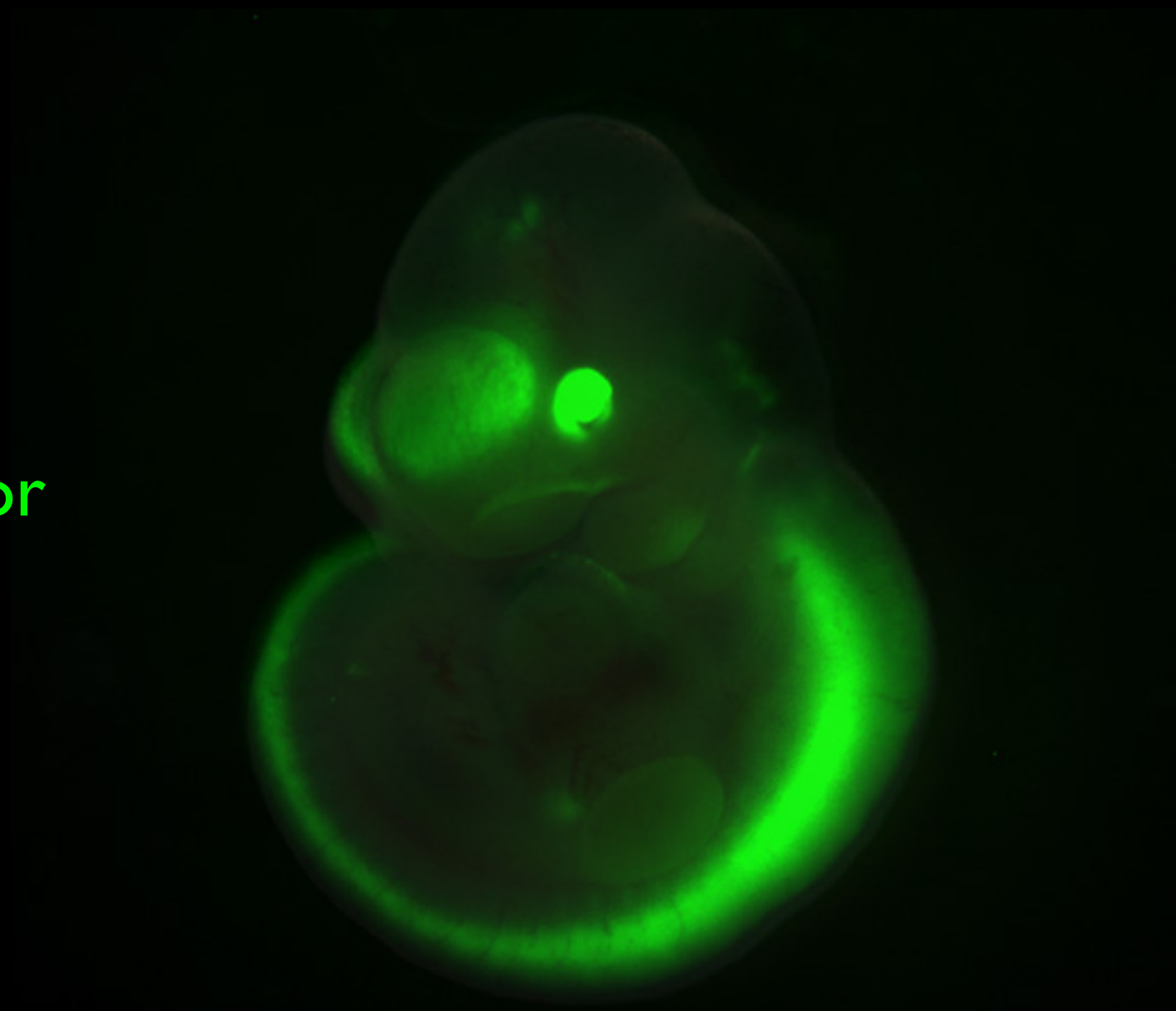
Four areas of biology by Tinbergen

FOUR AREAS OF BIOLOGY: FOUR QUESTIONS		Two objects of explanation	
		Developmental/historical A sequence that results in the trait	**Single form** The trait at one slice in time
Two kinds of explanations	**Proximate** Explains how organisms work by describing their mechanisms and their ontogeny	**Developmental Neurobiology**	**Mechanism** **Q: What is the structure of the trait; how does it work?** A: Description of the trait's anatomy, physiology, regulation, and how the trait works to accomplish a function.
	Evolutionary Explains how a species came to its current form by describing a sequence of forms, and how they were influenced by selection and other evolutionary factors.	**Evolutional Neurobiology**	**Adaptive significance** **Q: How have variations in the trait interacted with environments to influence fitness in ways that help to explain the trait's form?** A: Description of how variations in the trait have influenced fitness

A key factor

Pax6
transcription factor

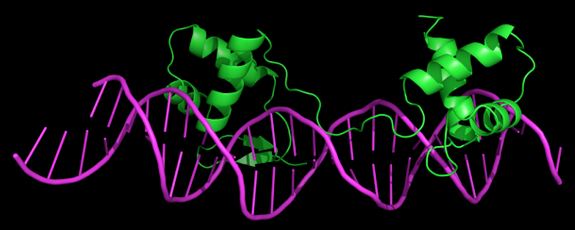




Pax-EGFP mouse@E10.5

Cortical Primordium

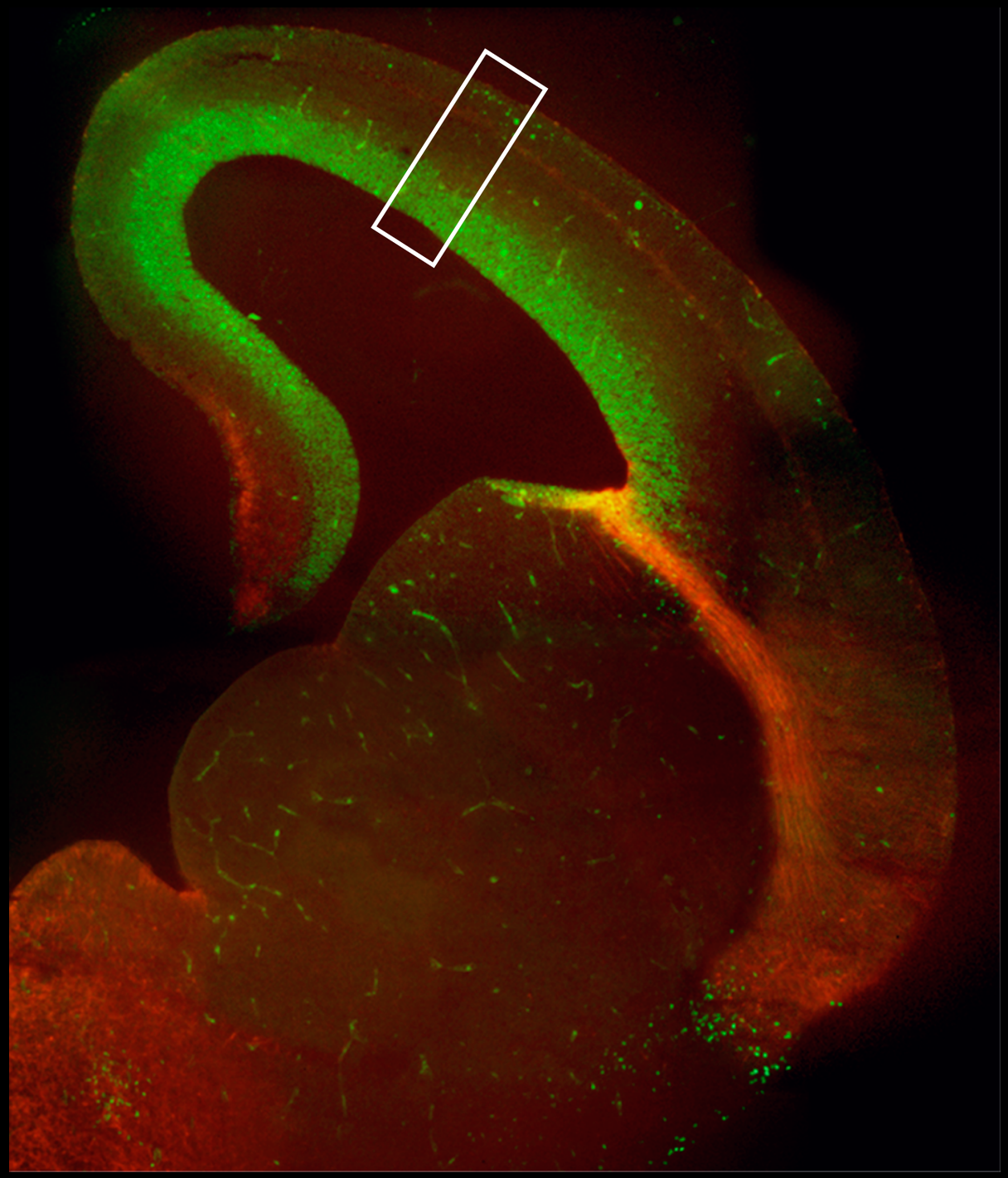
Pax6
transcription factor

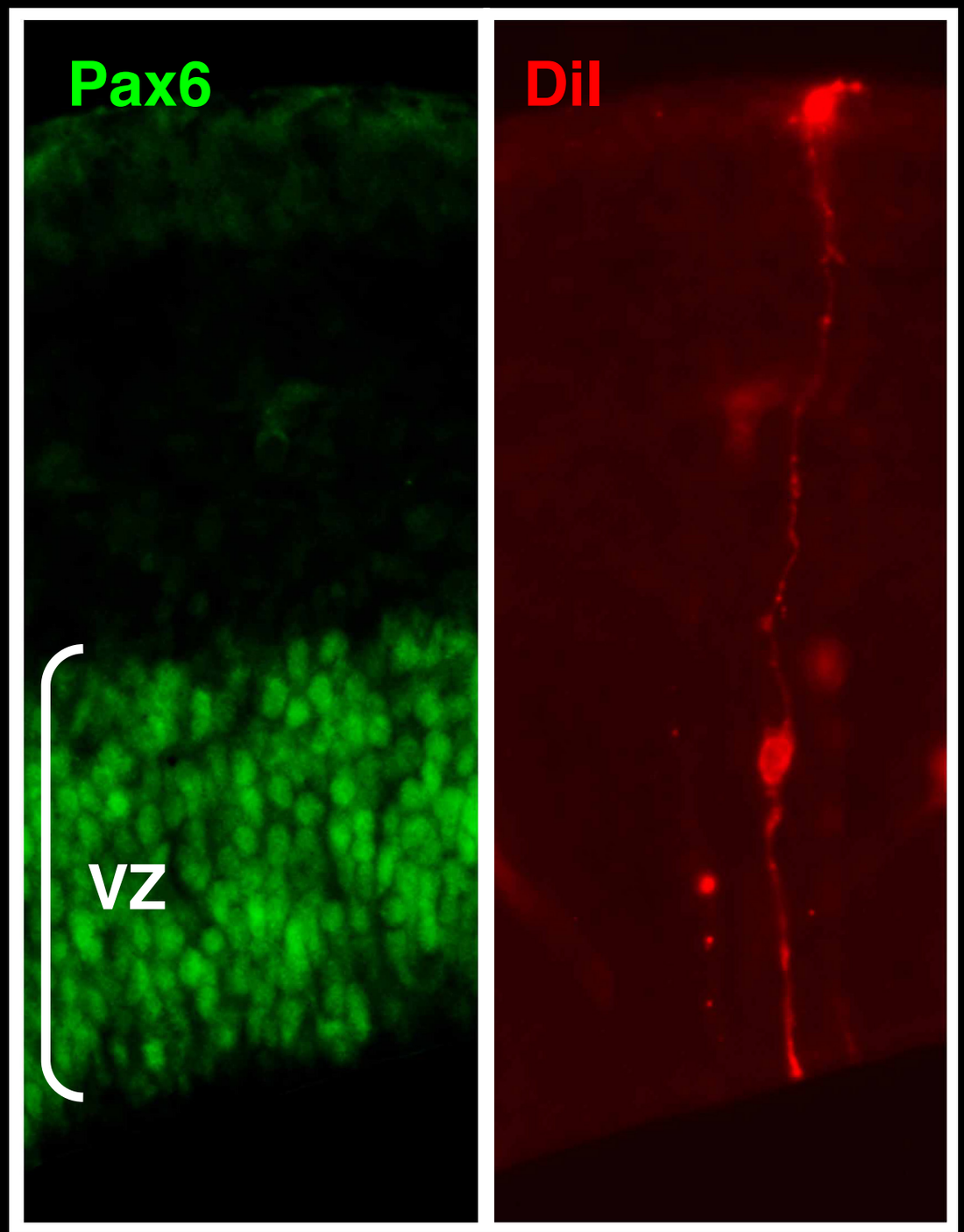


Pax6 is expressed in neural stem/progenitor cells

Tomioka et al., J Neurosci, 2000

Unique shape of radial progenitors



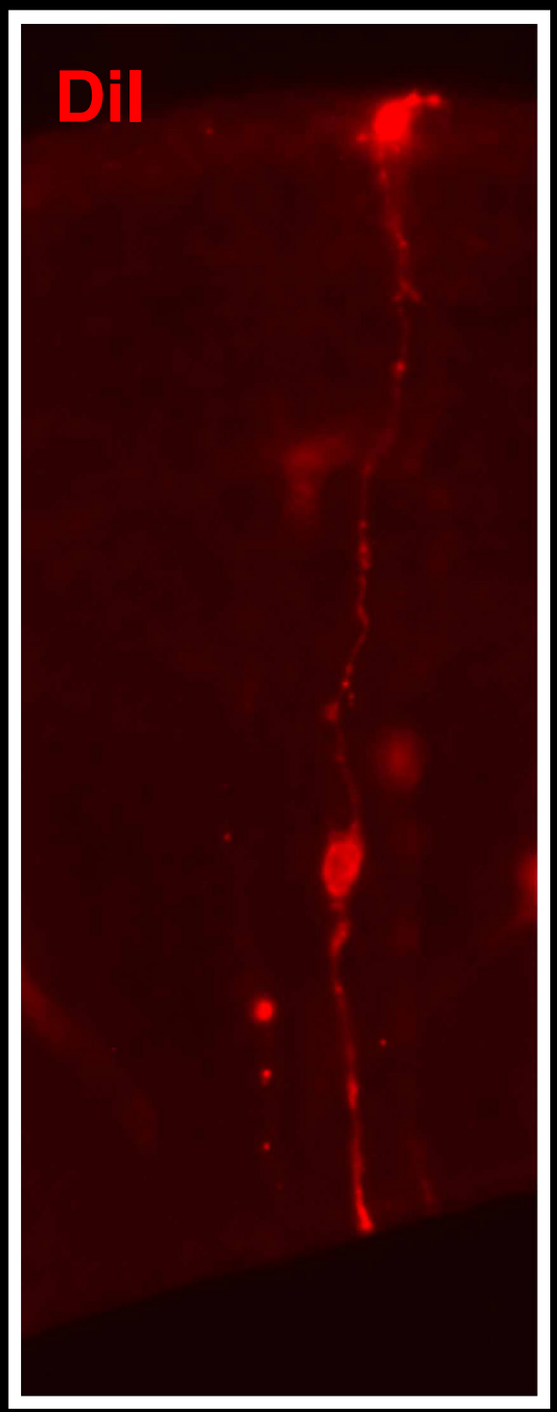


Taken by Dr. Miyata

Radial glia

- Highly polarized w/ long apical and basal processes
- Neural stem/progenitor cells
- Scaffold for neuronal migration

Mammalian RG

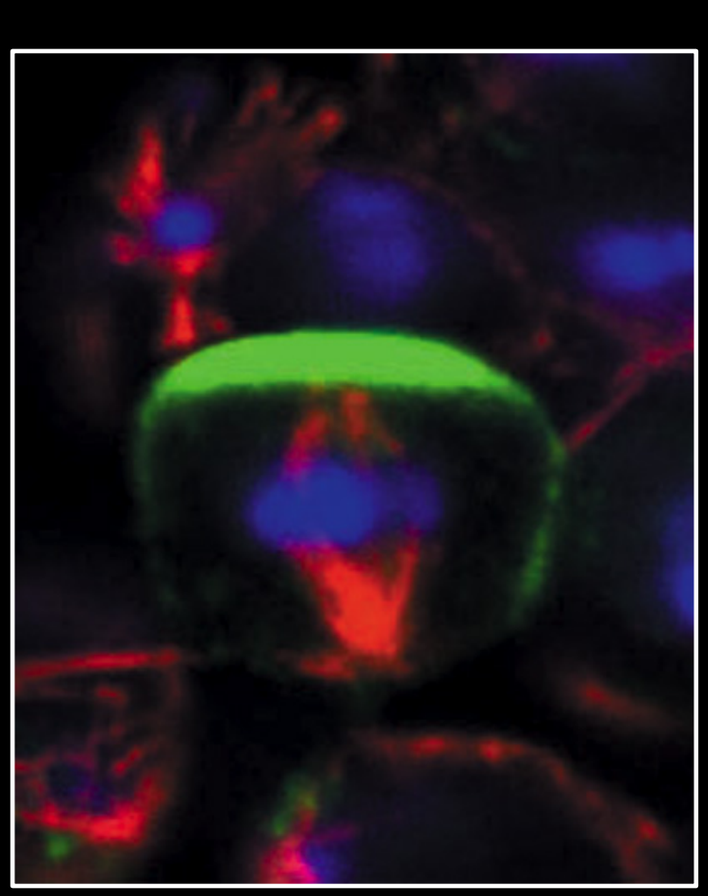


Radial glia

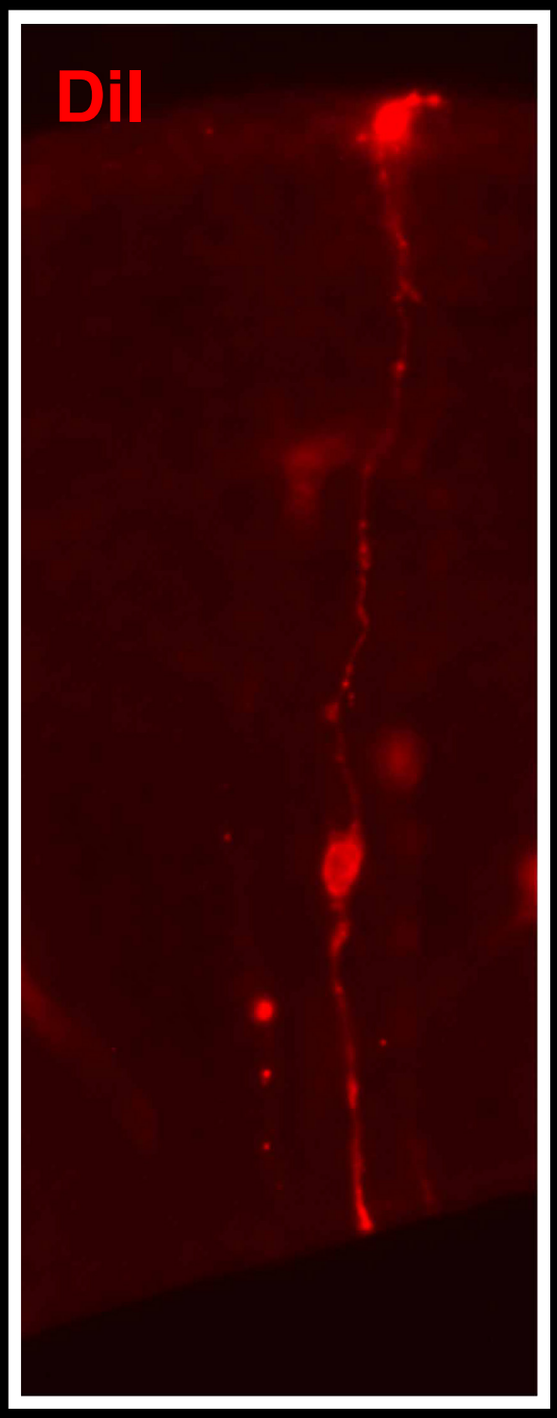
- Highly polarized w/ long apical and basal processes
- Neural stem/progenitor cells
- Scaffold for neuronal migration

Fly NSCs

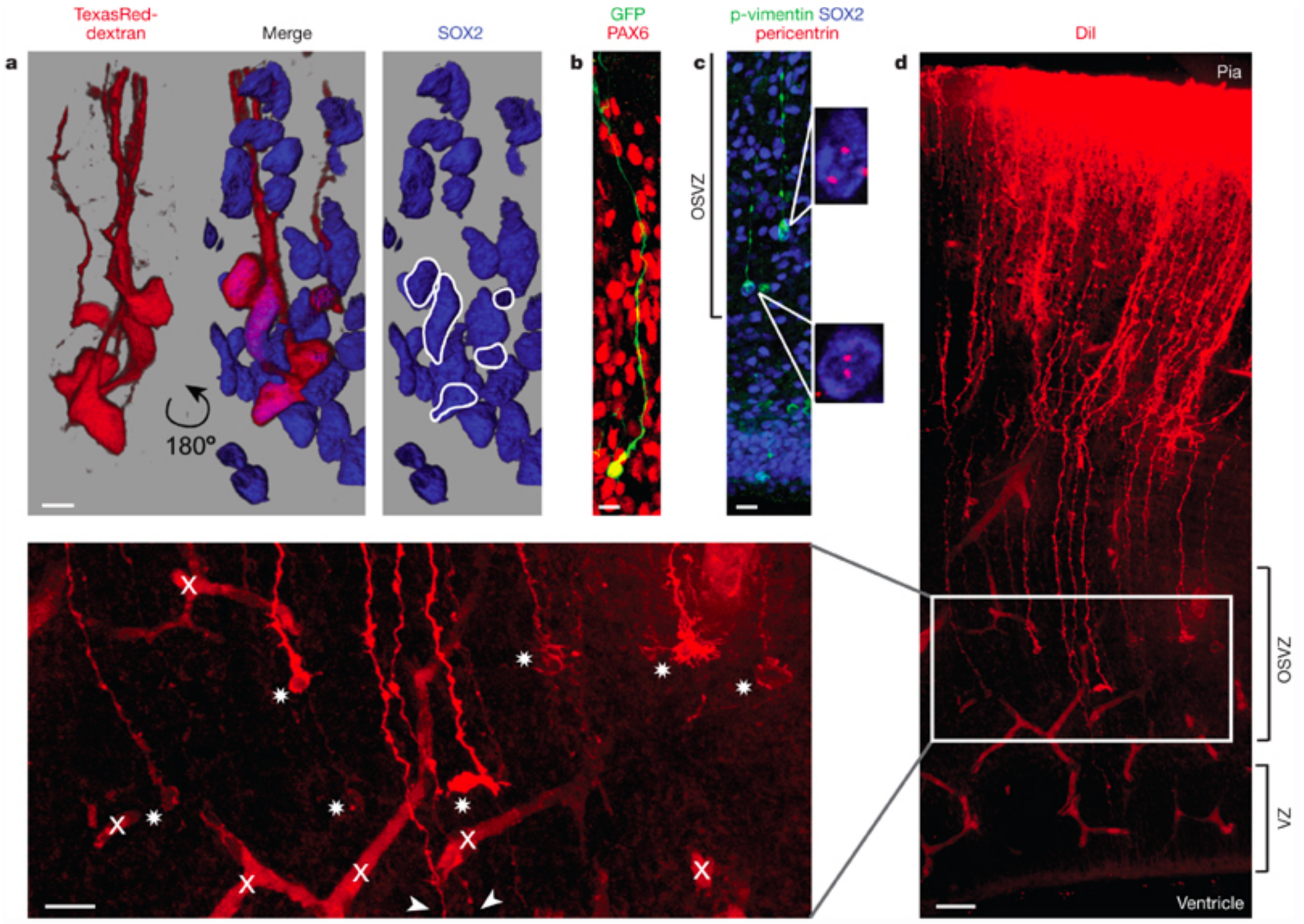
From Matsuzaki Lab
HP@ CDB



Mammalian RG

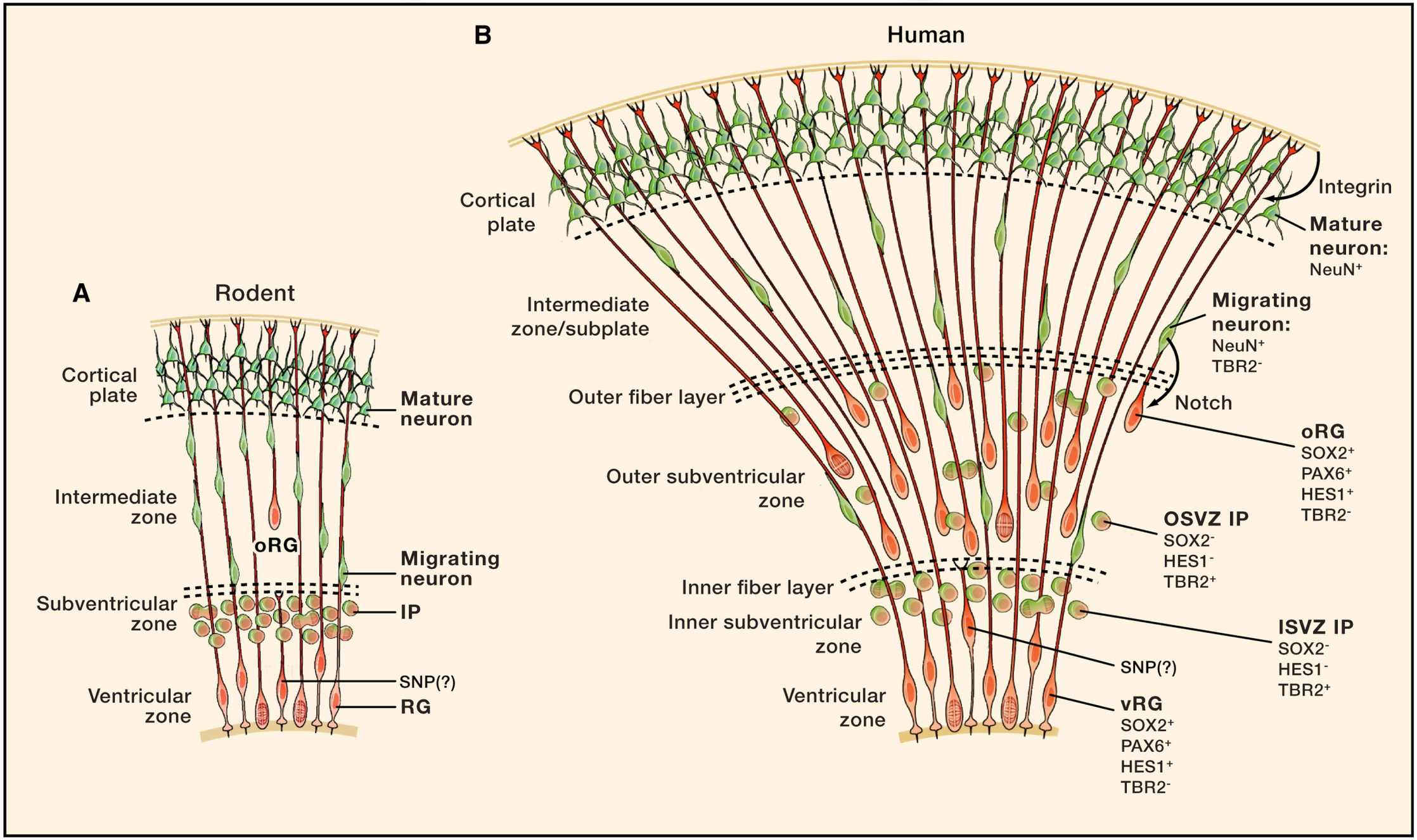


Basal processes of NPCs in primate OSVZ



Hansen et al.: Neurogenic radial glia in the outer subventricular zone of human neocoretex. Nature, 2010

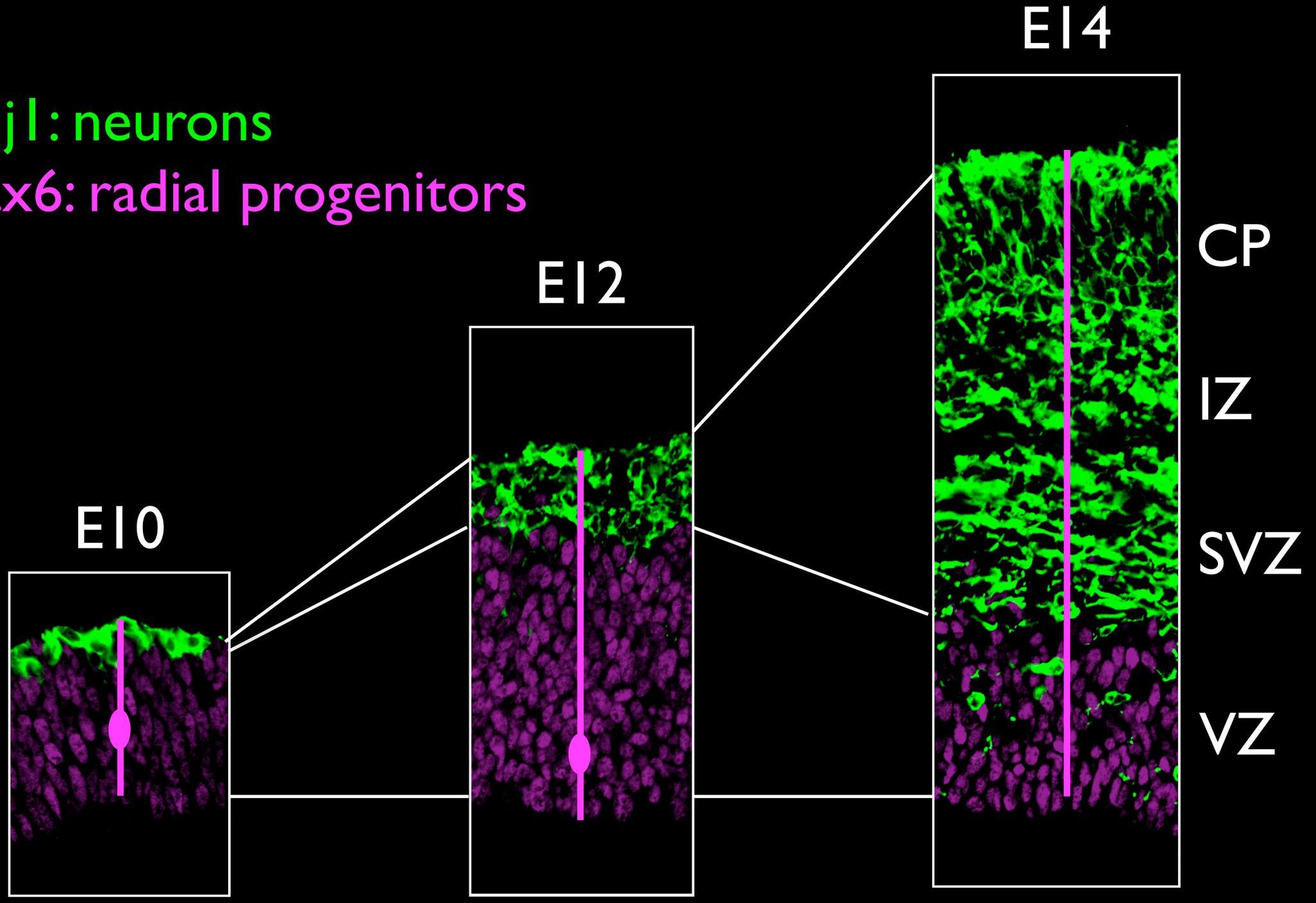
Unique shape of RG: a key to corticogenesis



Lui et al.: Development and evolution of the human neocortex. Cell, 2011

RG become longer & longer…

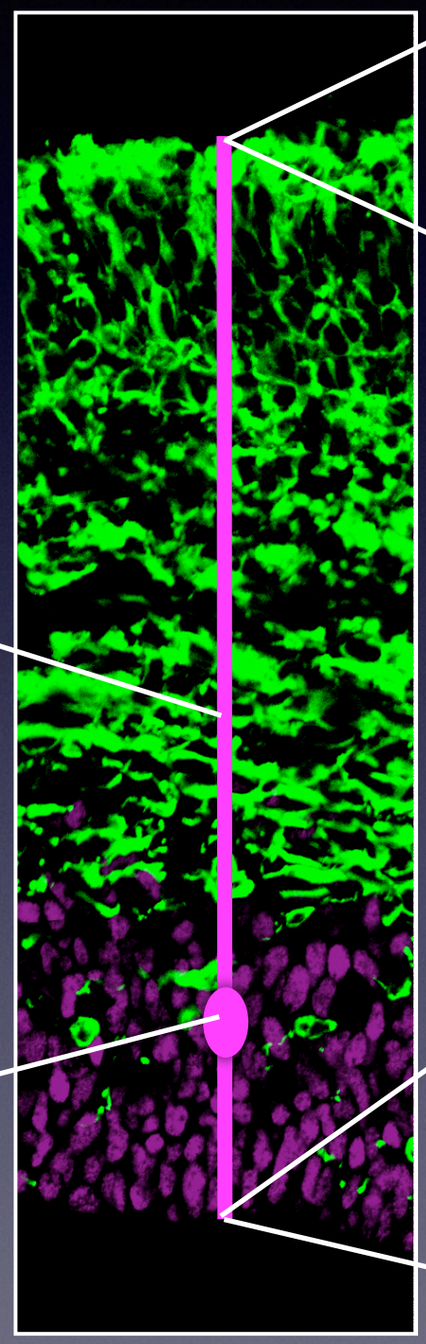
Tuj1: neurons
Pax6: radial progenitors



Symmetric division Asymmetric division

Molecules working in/around the radial glia

Tuj I : neurons
Pax6: RG



Basal molecules

- Secreted molecules
- Integrins
- Cyclin D2, FMRP

Radial glial molecules

- Fabp7/BLBP
- LewisX/CD15
- Notch signals

Nuclear molecules

- TFs incl. Pax6, Ngn2, Dmrta1
- Polycombs
- BAF complex

Apical molecules

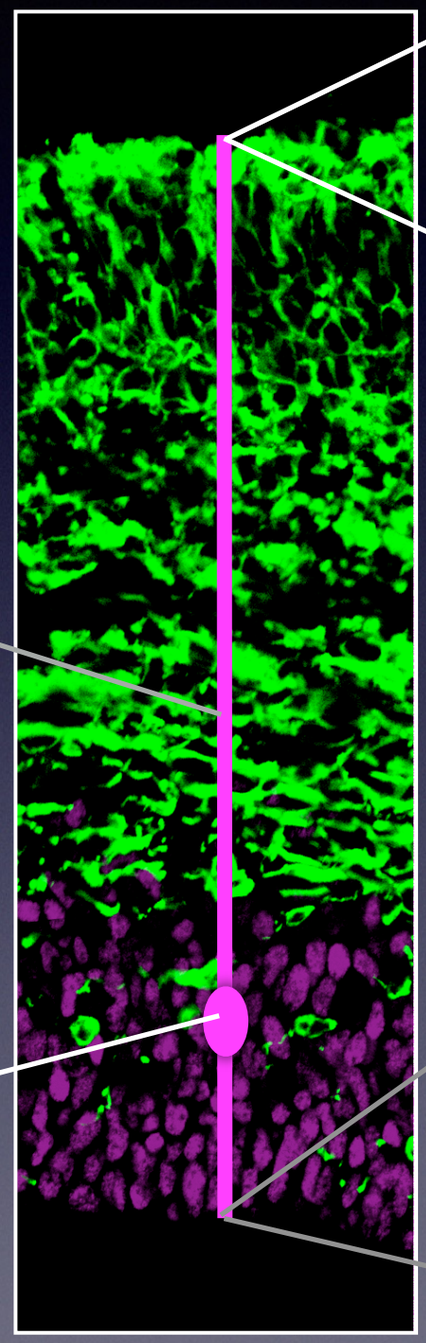
- δ-catenin, FMRP
- Polarity proteins
- Centrosomal proteins

Basal molecules

Secreted molecules

Integrins

Cyclin D2, FMRP



Radial glial molecules

Fabp7/BLBP

LewisX/CD15

Notch signals

Nuclear molecules

TFs incl. Pax6, Ngn2, Dmrta1

Polycombs

BAF complex

Apical molecules

δ-catenin, FMRP

Polarity proteins

Centrosomal proteins

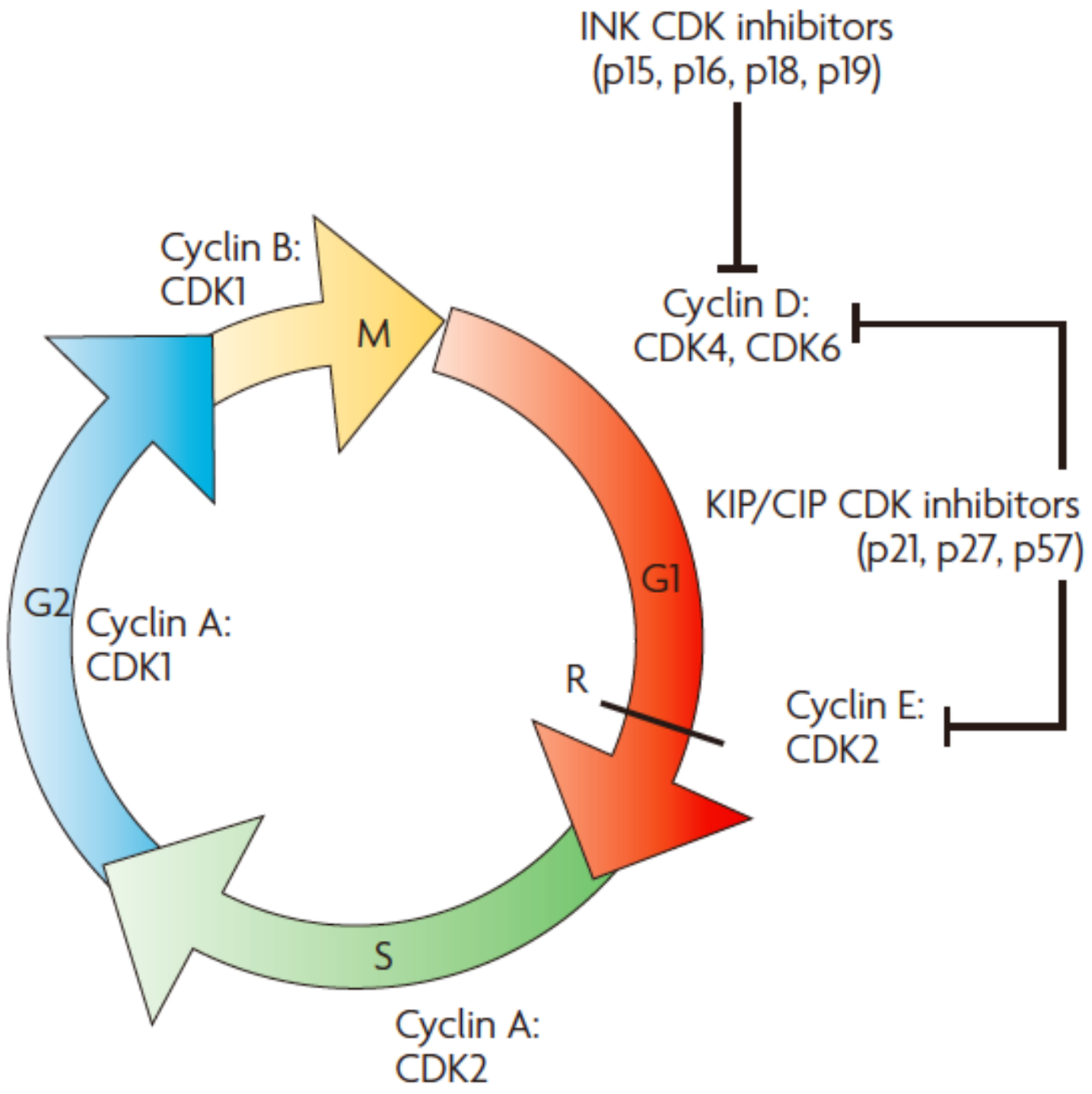
Cell cycle regulator: Cyclin

Cyclin D1 ablation

- lengthens G1 phase
- increase differentiation

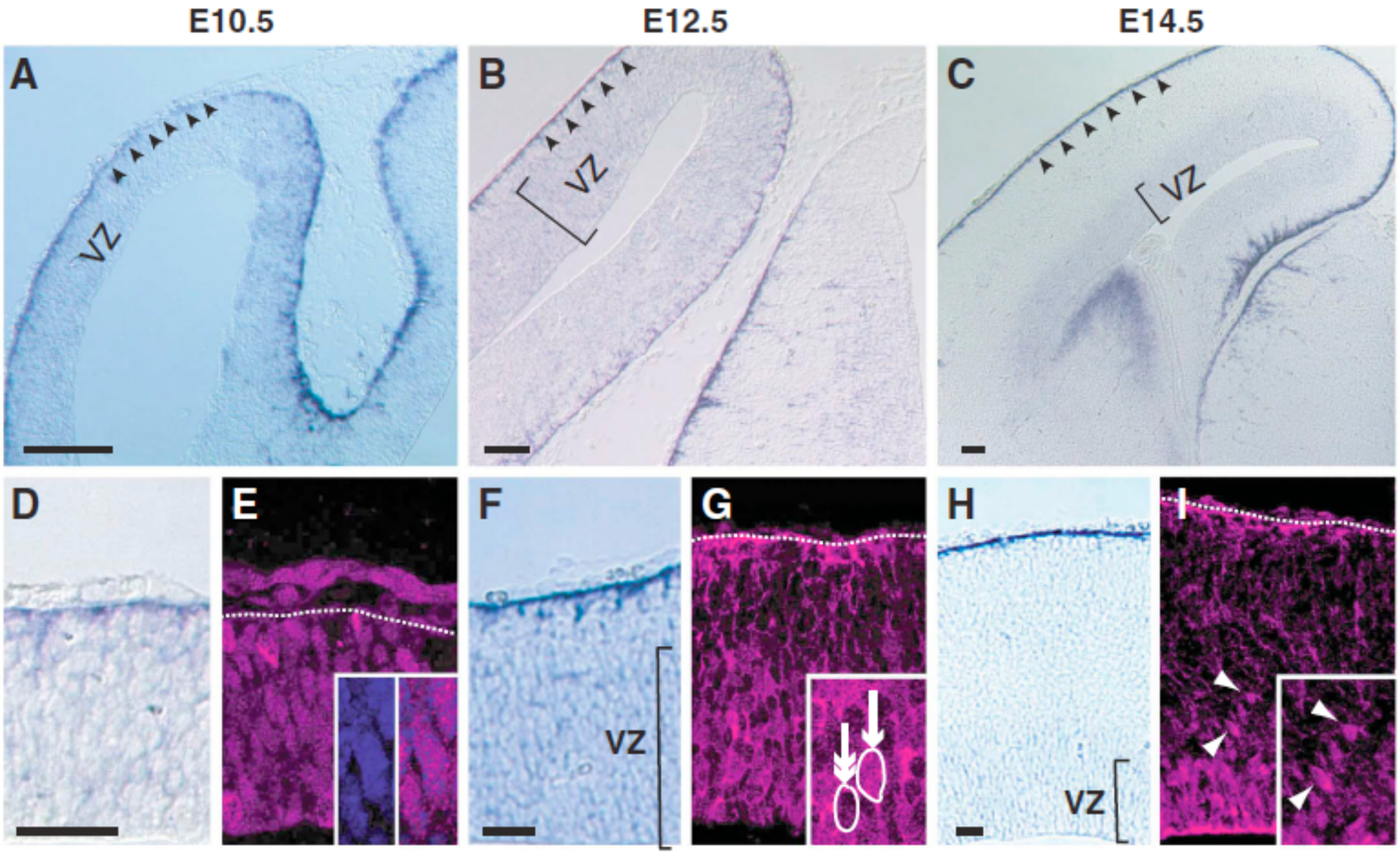
Cyclin D2 ablation

- lengthens G1 phase
- induces differentiation
- reduces cortical thickness

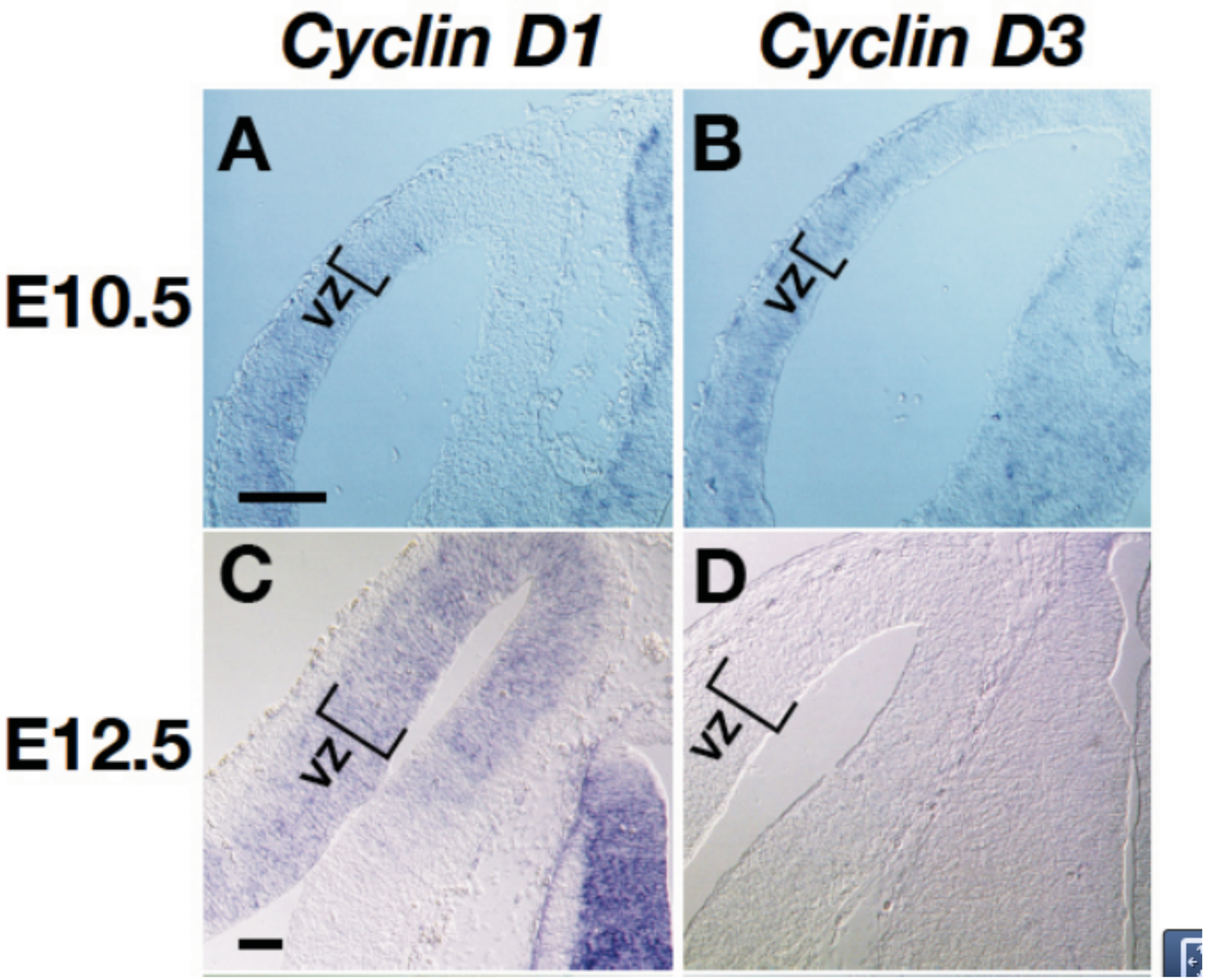


Dehay and Kennedy et al., 2007; Lange et al., 2009; Glickstein et al., 2009; Pilaz et al., 2009

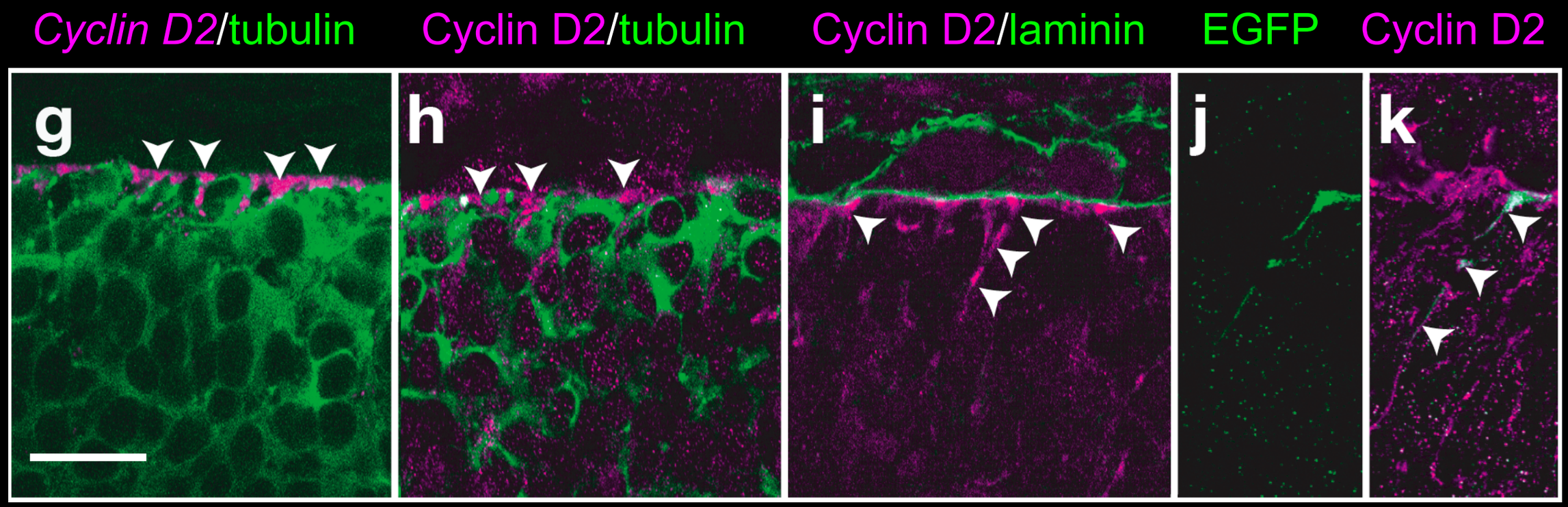
Cyclin D2 localization at the basal endfoot



Tsunekawa et al., EMBO J, 2012

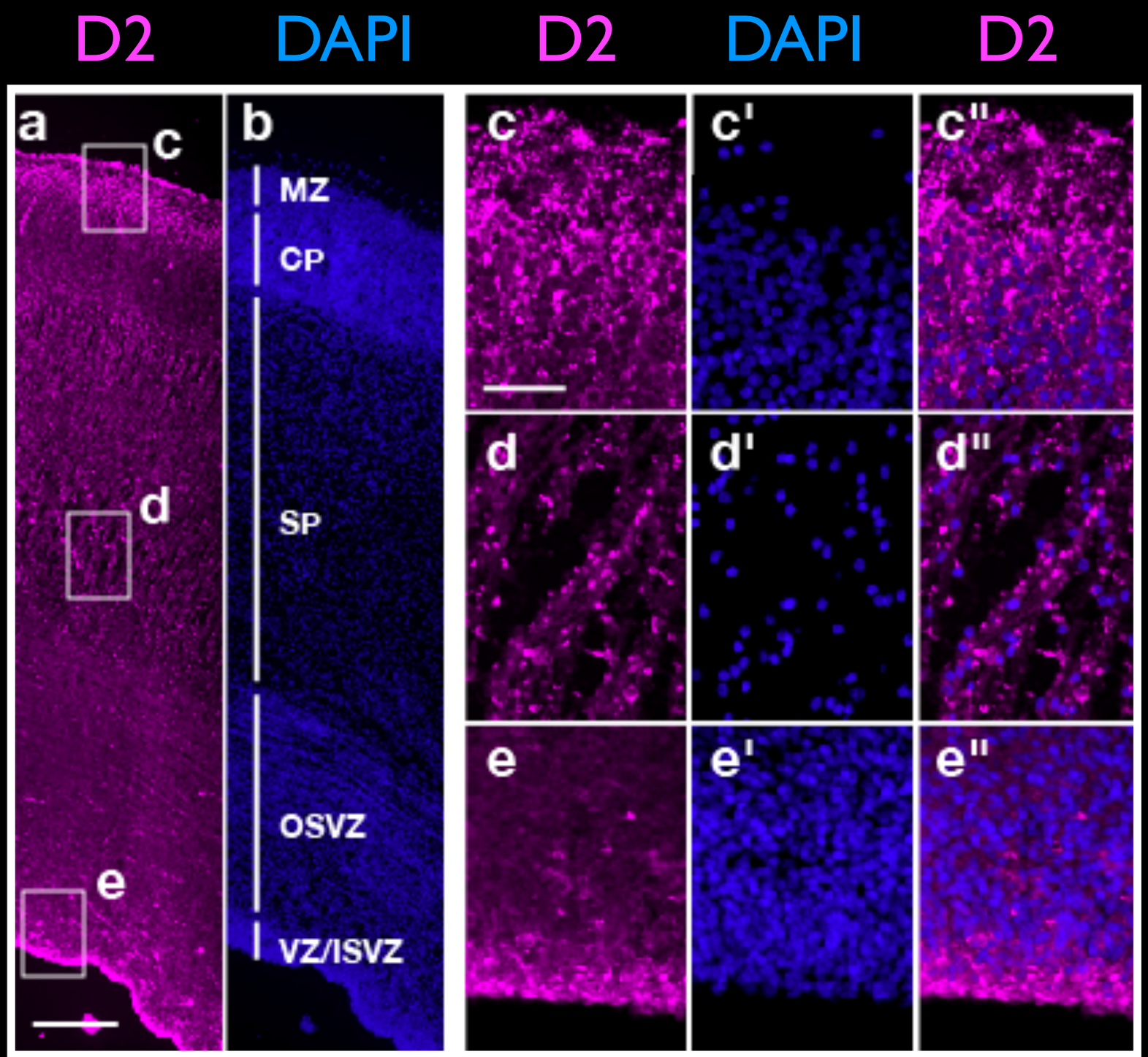

Cyclin D1
Cyclin D3
E10.5
E12.5
A
B
C
D
vz
vz
vz
vz

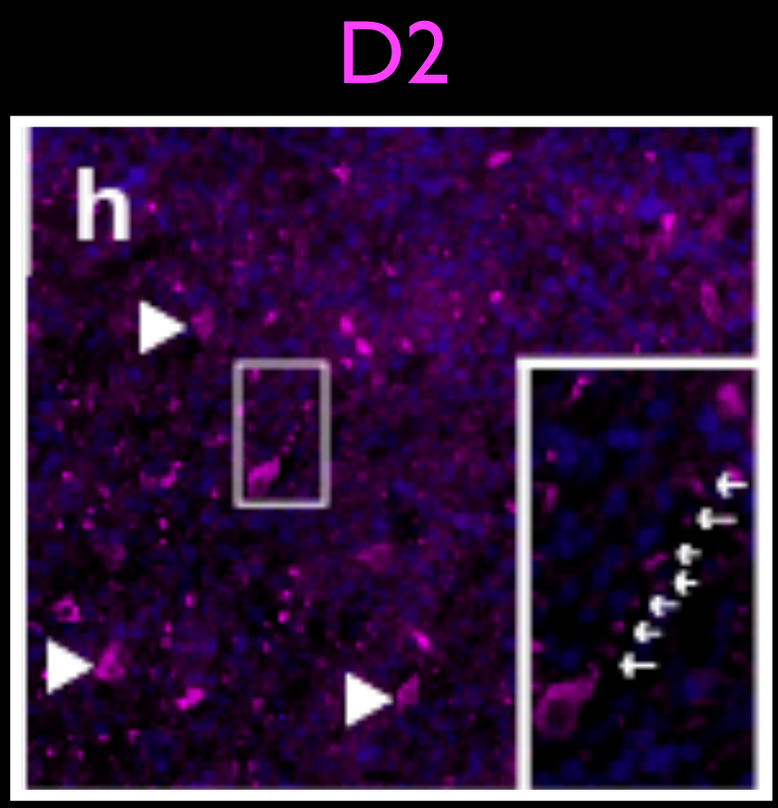
Cyclin D2 localization at basal endfeet



E14.5 mouse

Similar Cyclin D2 expression in human fetal ctx



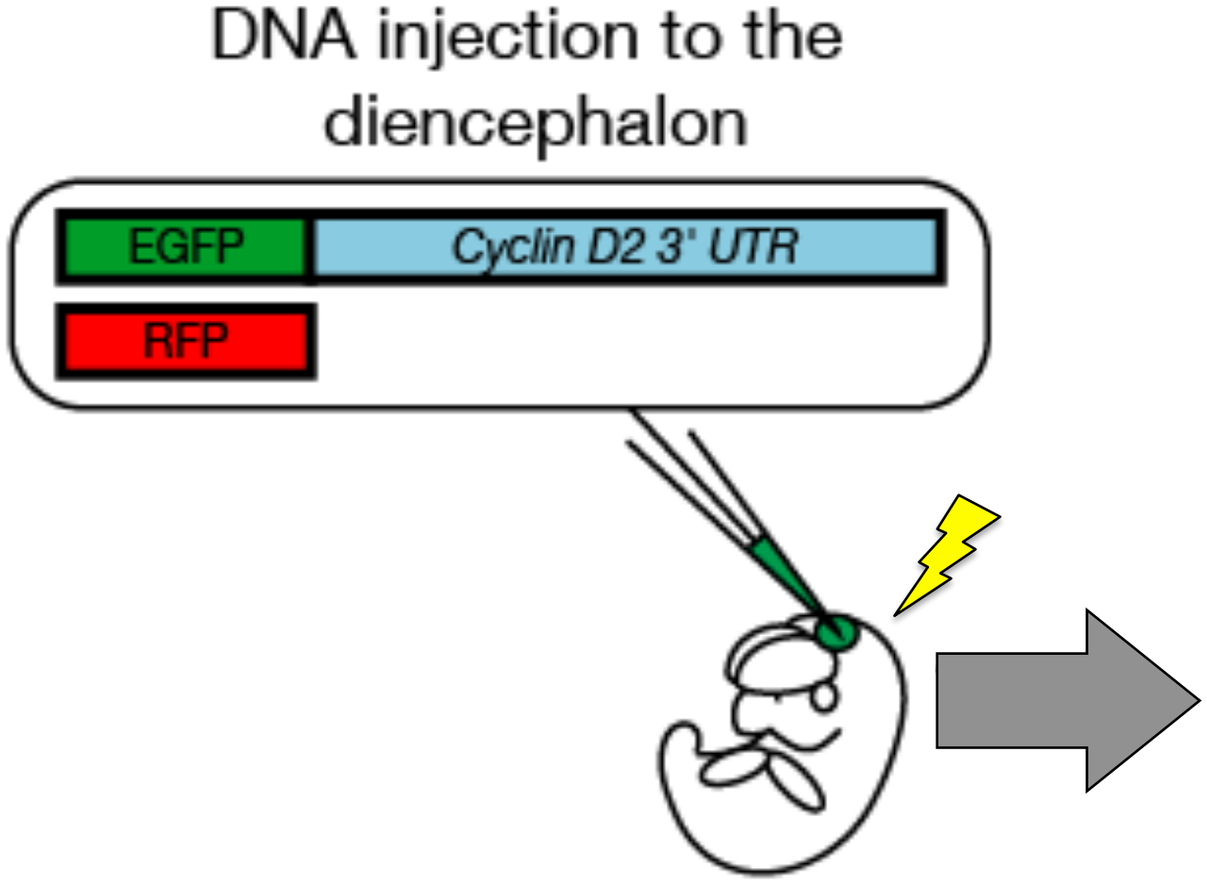


Human fetal brain @GW19

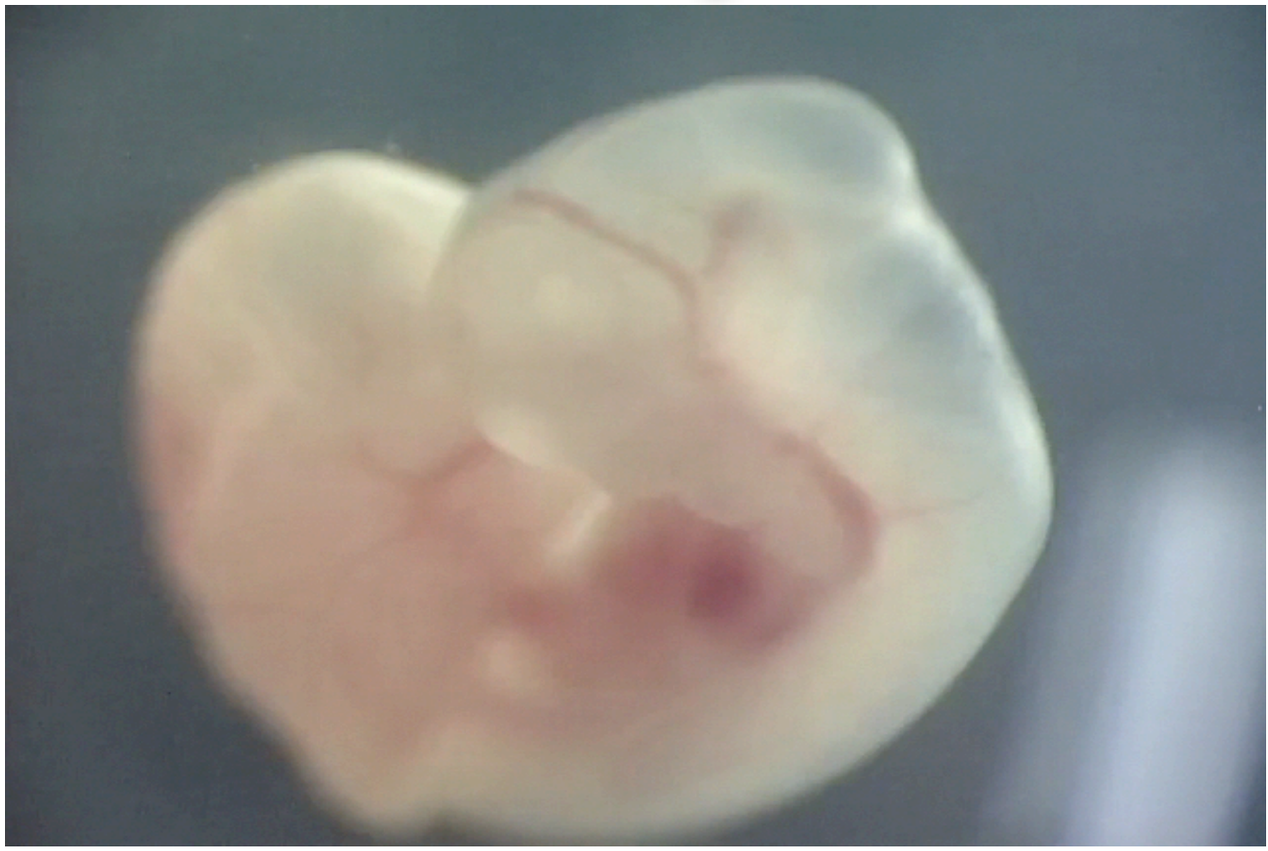
In collaboration w/ Dr. Seong-Seng Tan

How basal Cyclin D2 mRNA is transported basally?

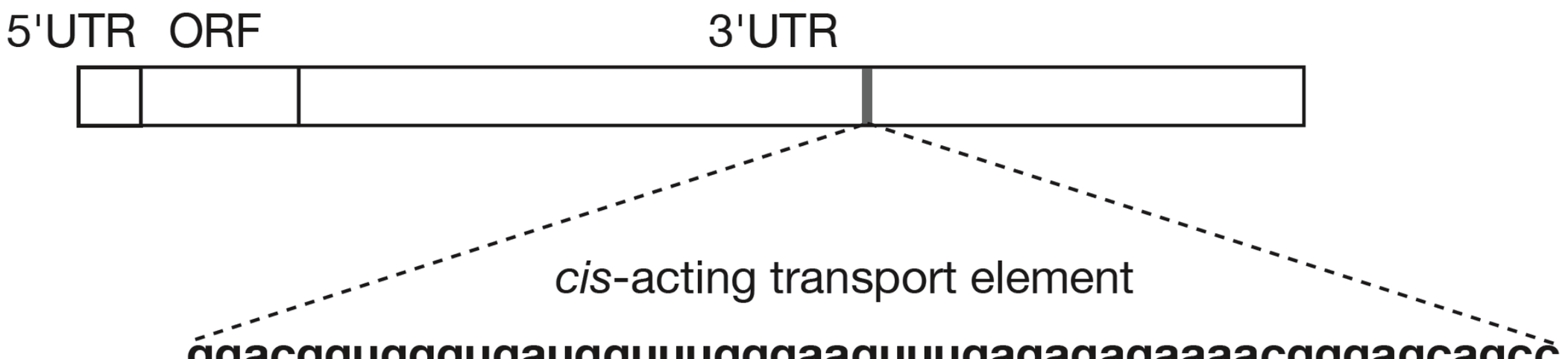
A *cis*-acting transport element of *Cyclin D2* mRNA resides in its 3' UTR?

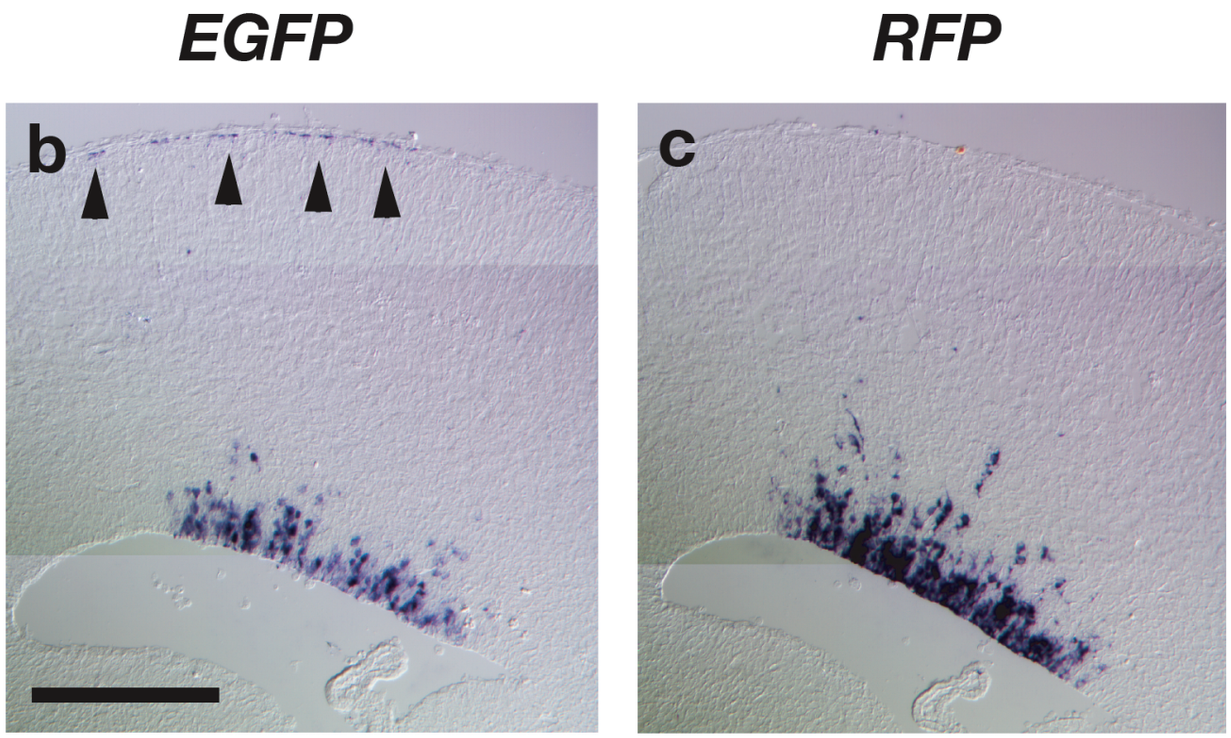


Whole embryo culture



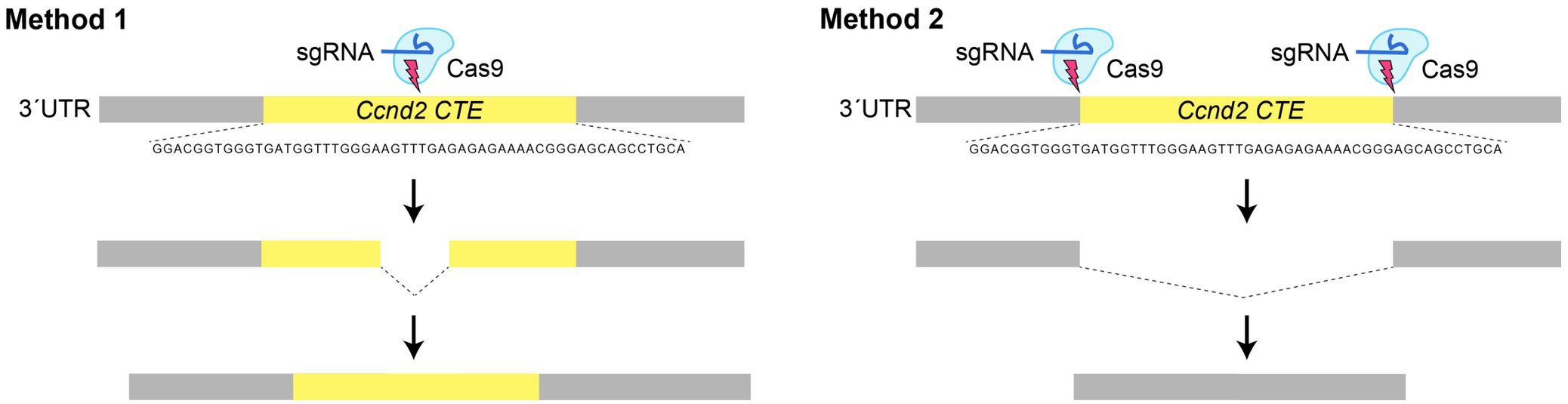
A 50 bp *cis*-acting transport element of *Cyclin D2* mRNA in its 3' UTR

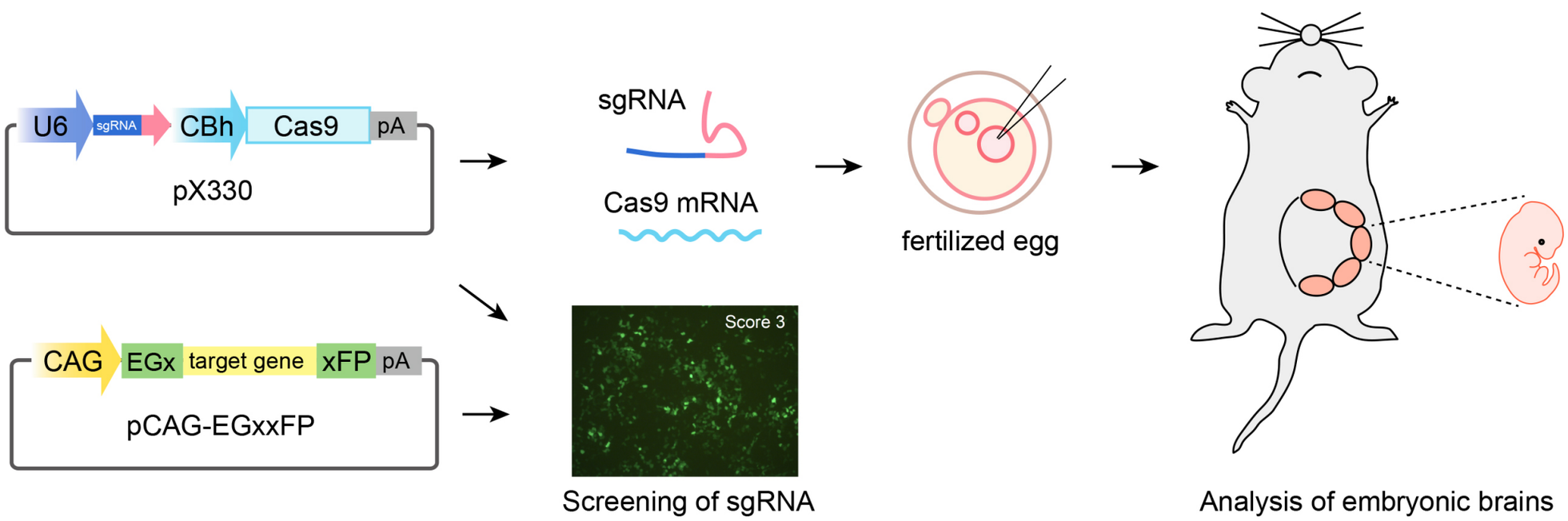




Tsunekawa et al., EMBO J, 2012

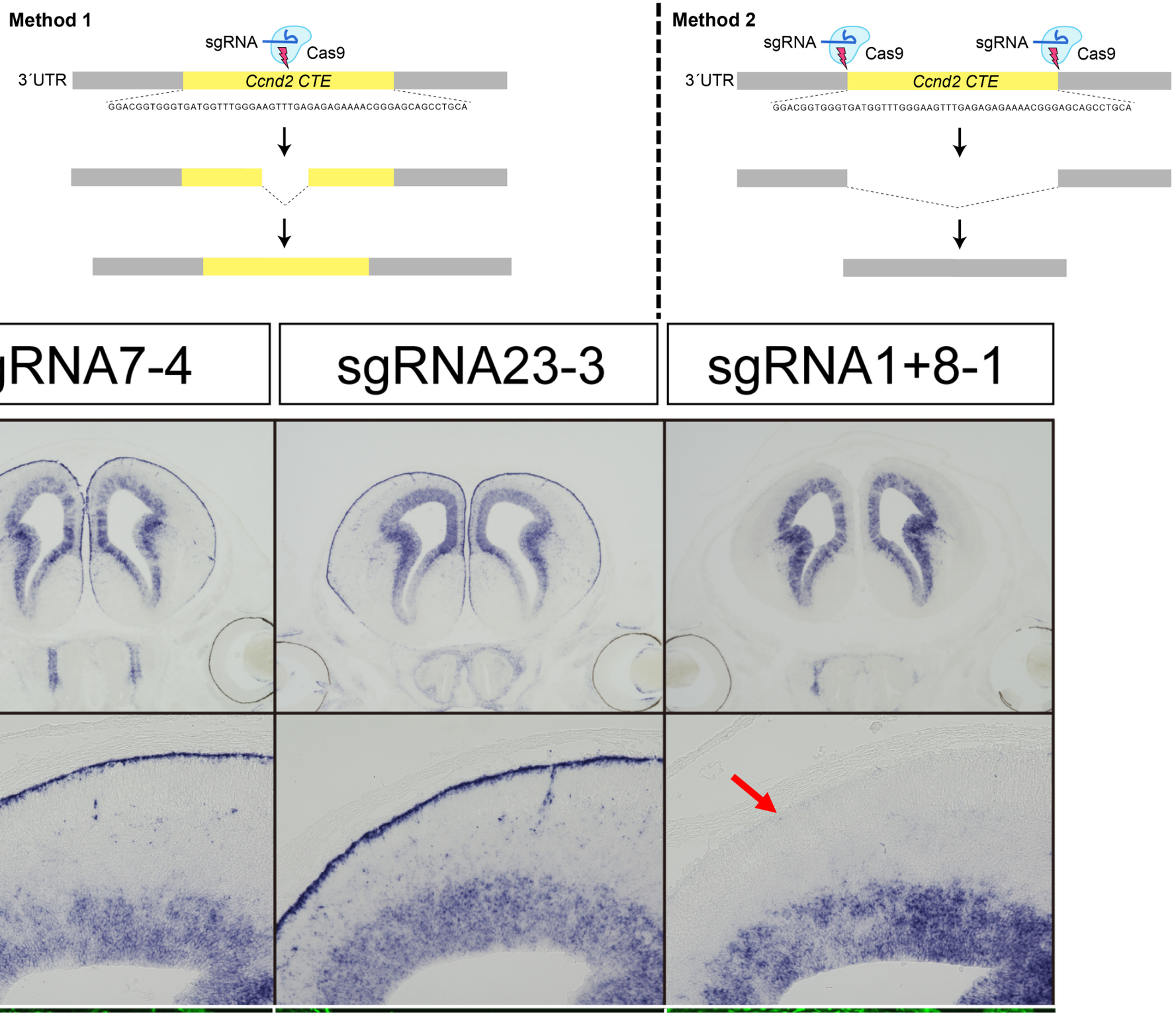
Deletion of *Cyclin D2 cis*-element





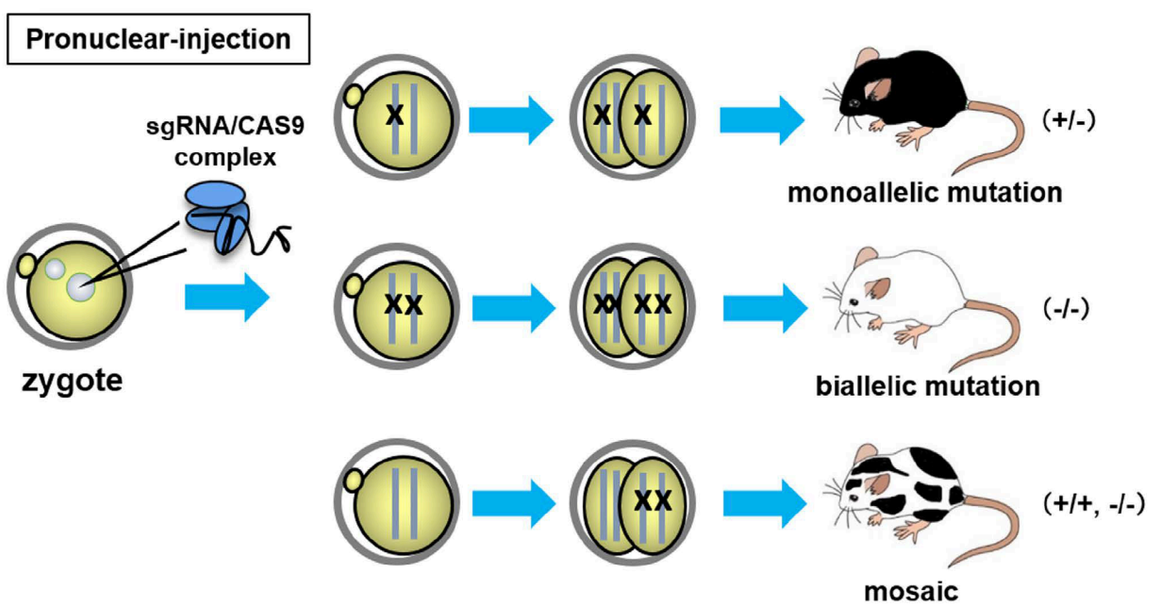
Dr. Kikkawa collaboration w/
Dr. Inoue@NCNCP

Ablation of *Cyclin D2* basal localization

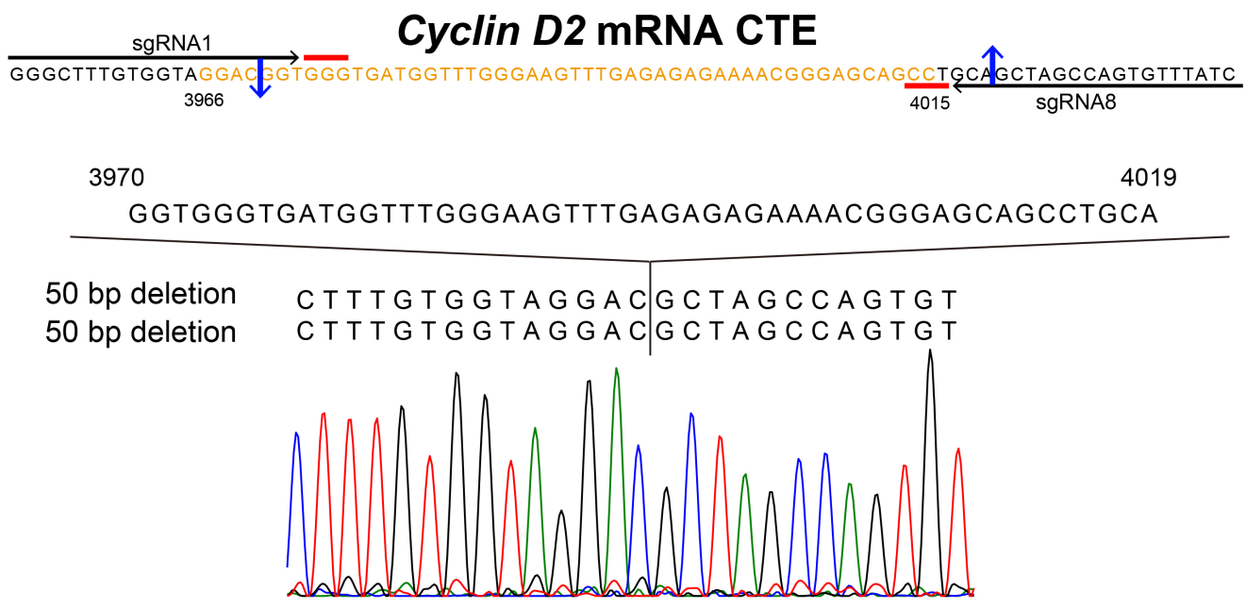


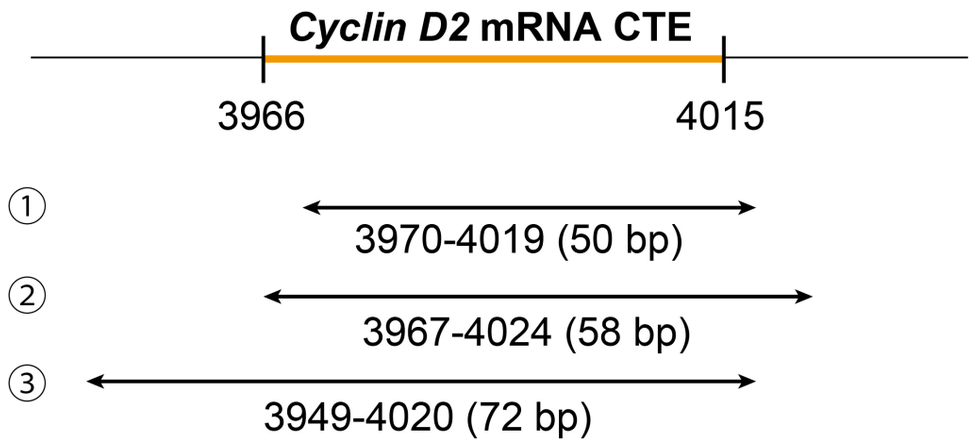
Kikkawa, unpublished

Making F1 generation to avoid mozaichism

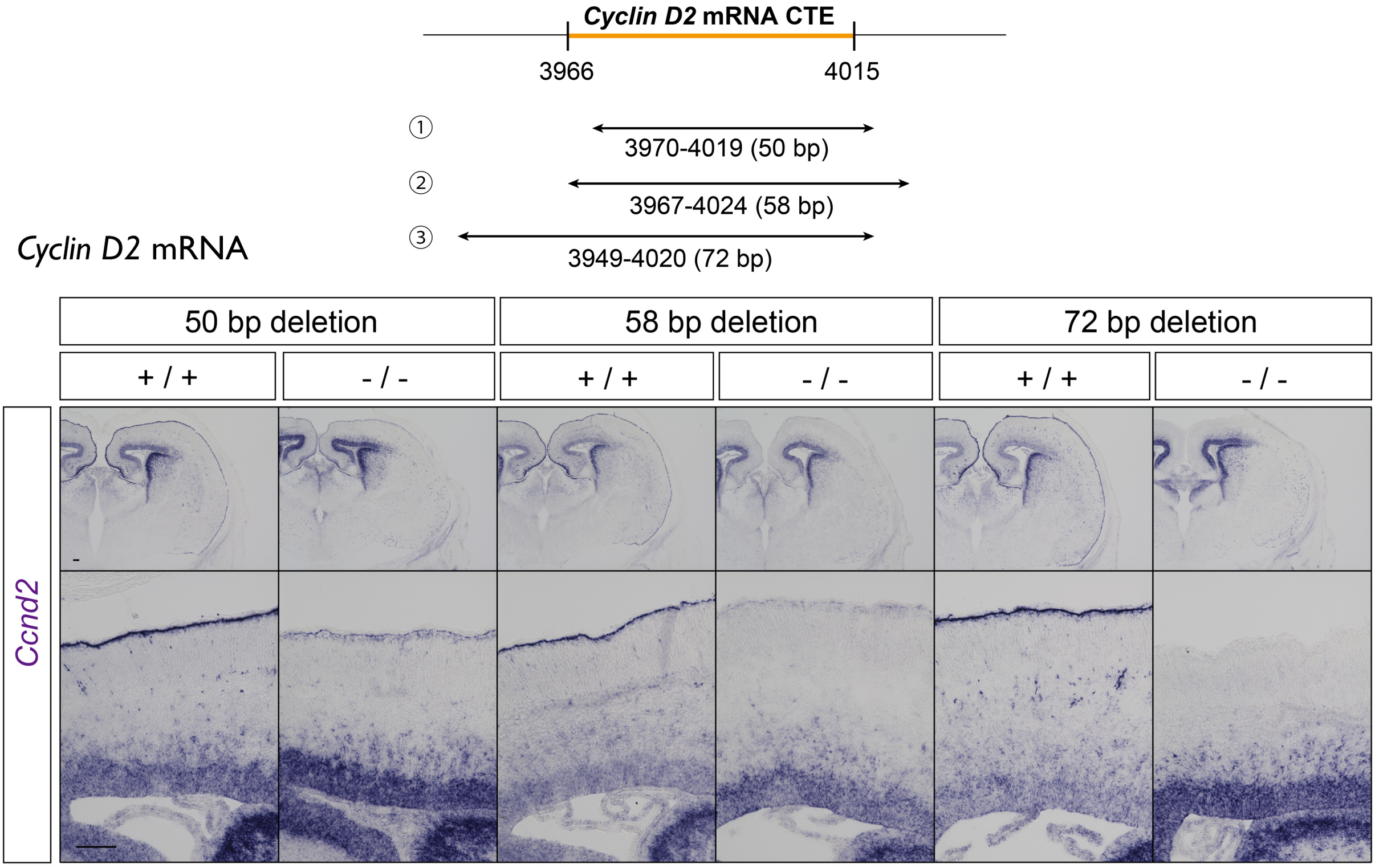


Oji et al., 2016





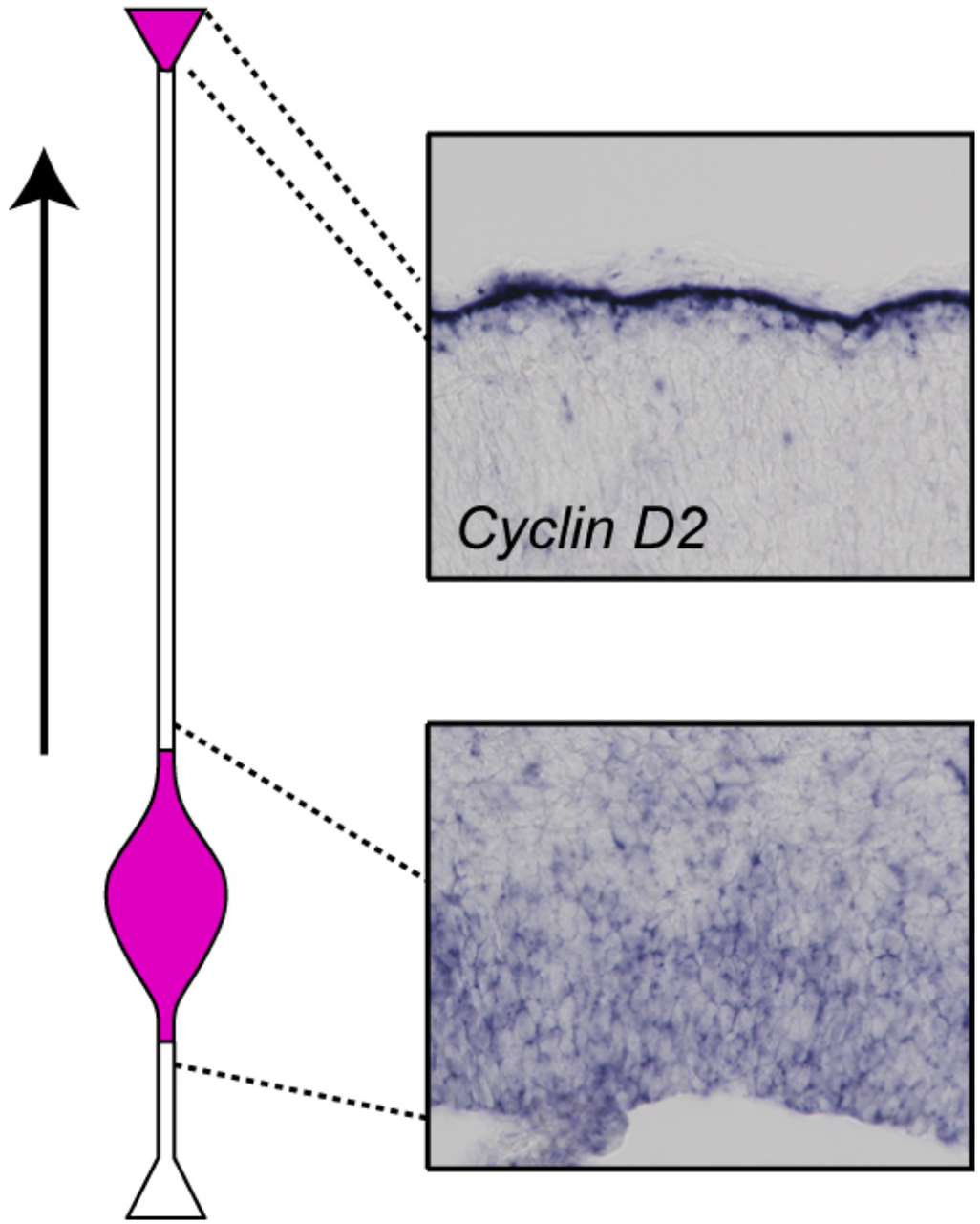
⊿CTE mutant generated by genome editing



Kikkawa, unpublished

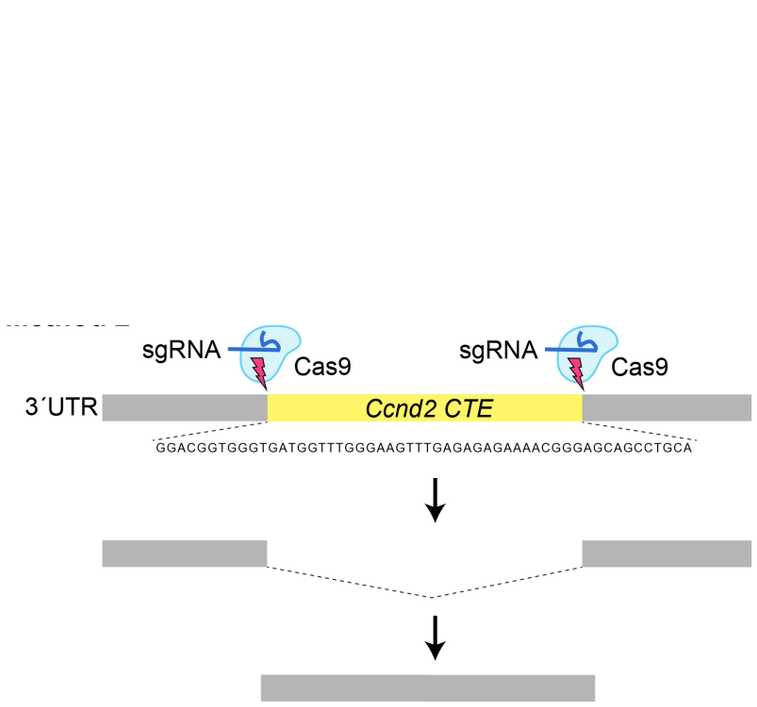
@E16.5

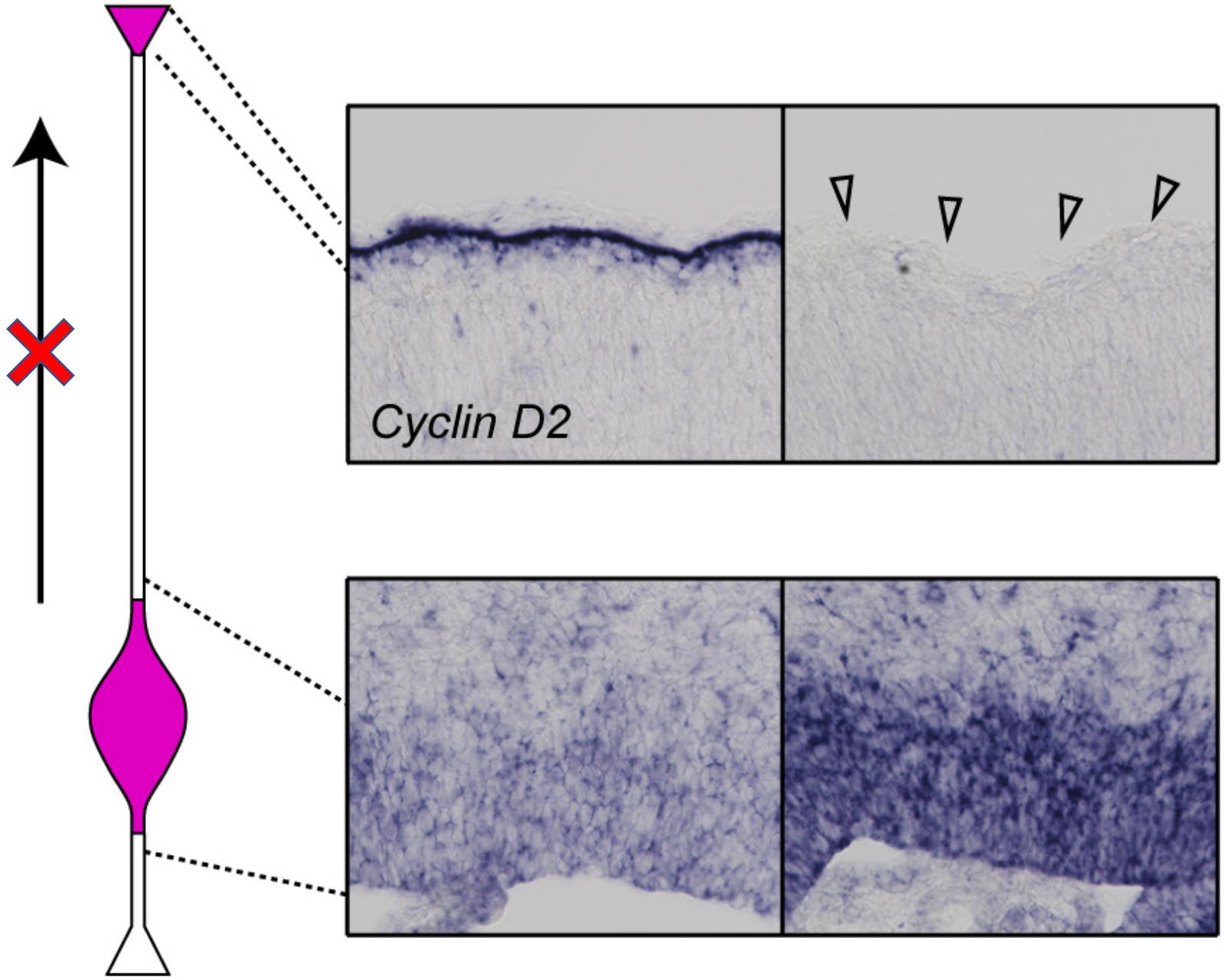
⊿CTE mutant generated by genome editing



Kikkawa, unpublished

⊿CTE mutant generated by genome editing

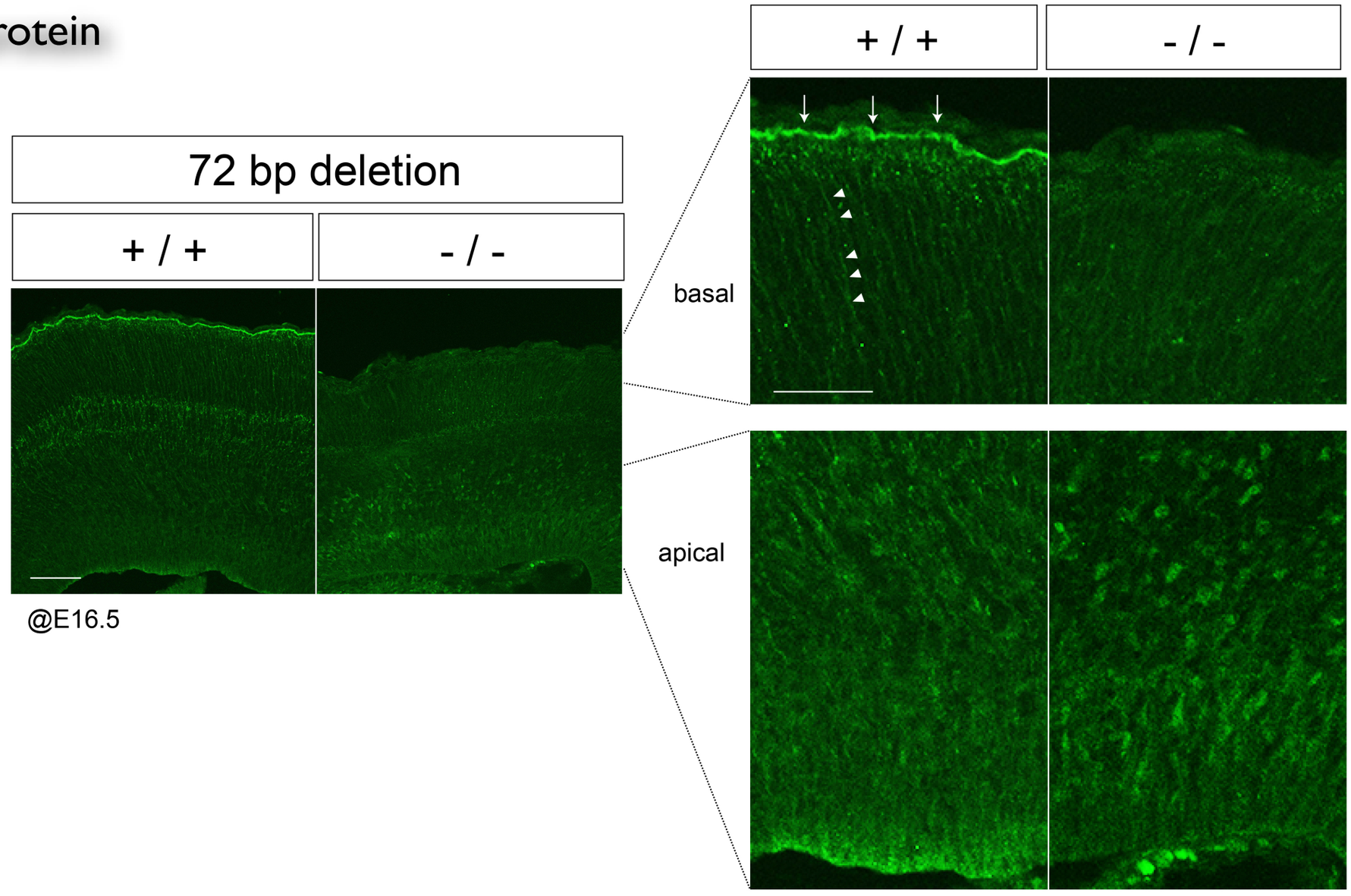




Kikkawa, unpublished

⊿CTE mutant generated by genome editing

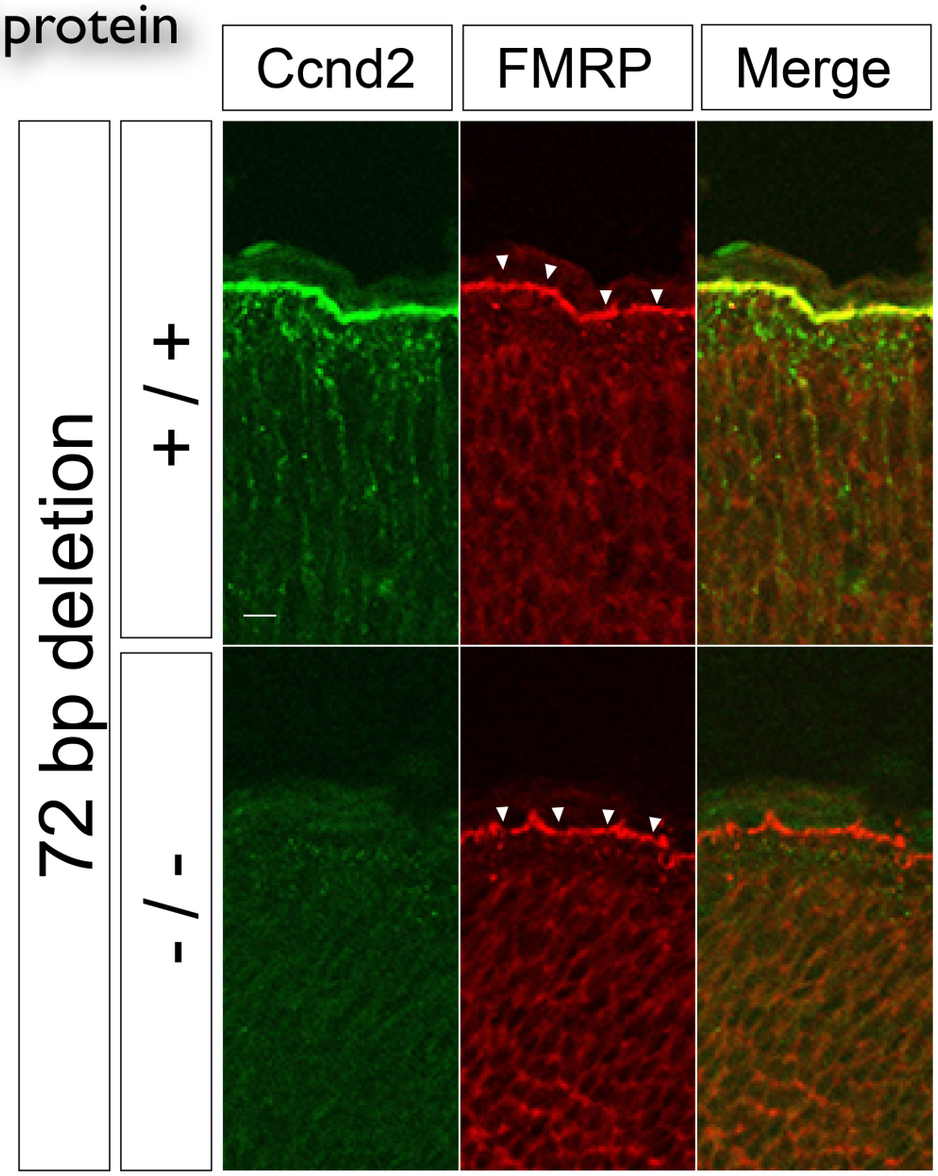
Cyclin D2 protein



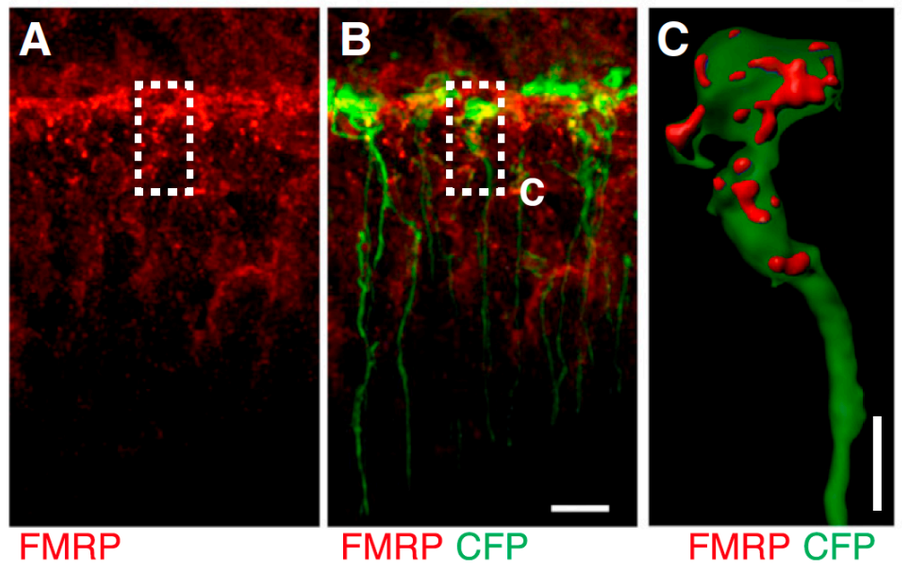
Kikkawa, unpublished

⊿CTE mutant generated by genome editing

Cyclin D2 protein



FMRP (Fragile X mental retardation protein)
: RNA binding protein

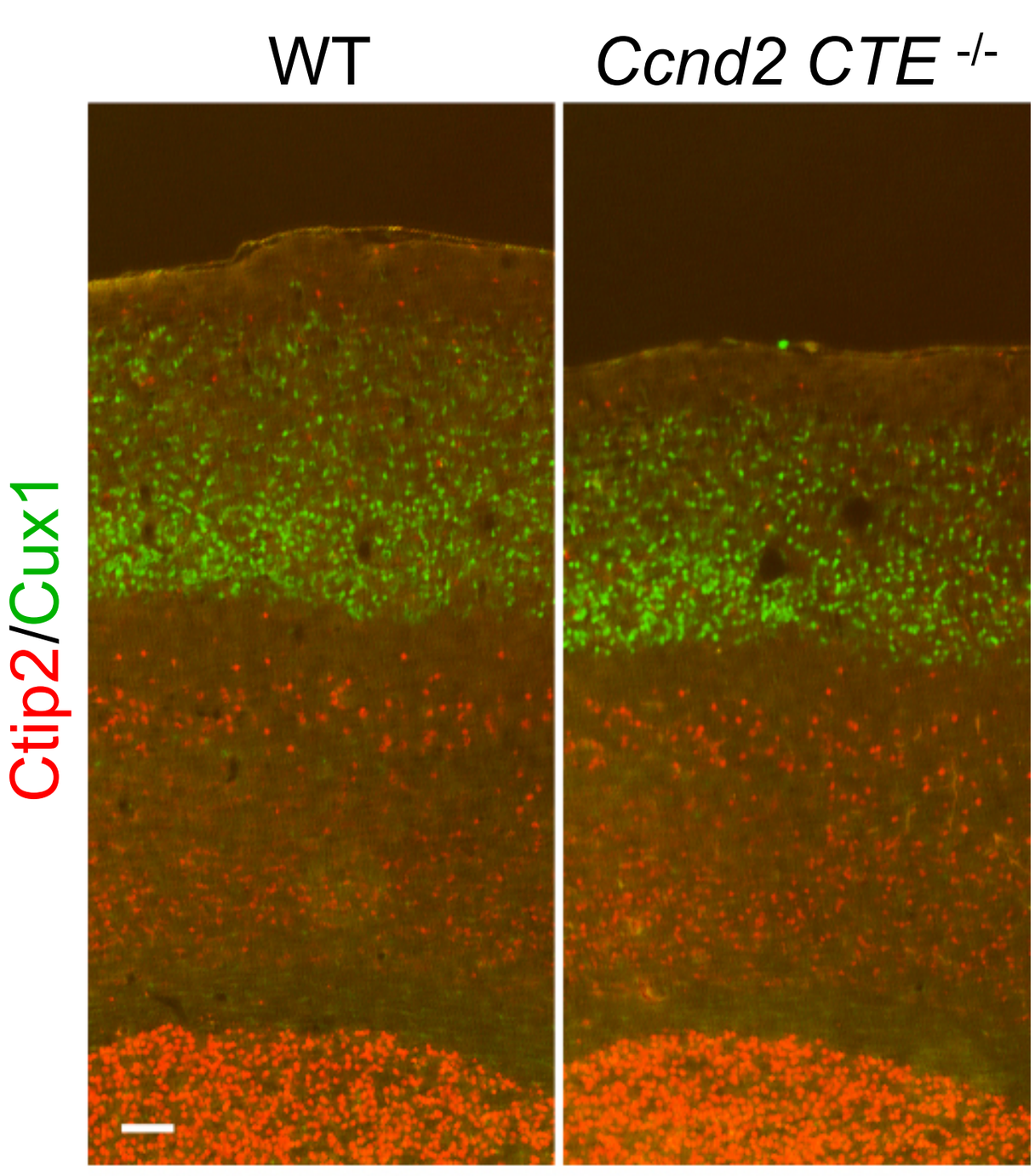


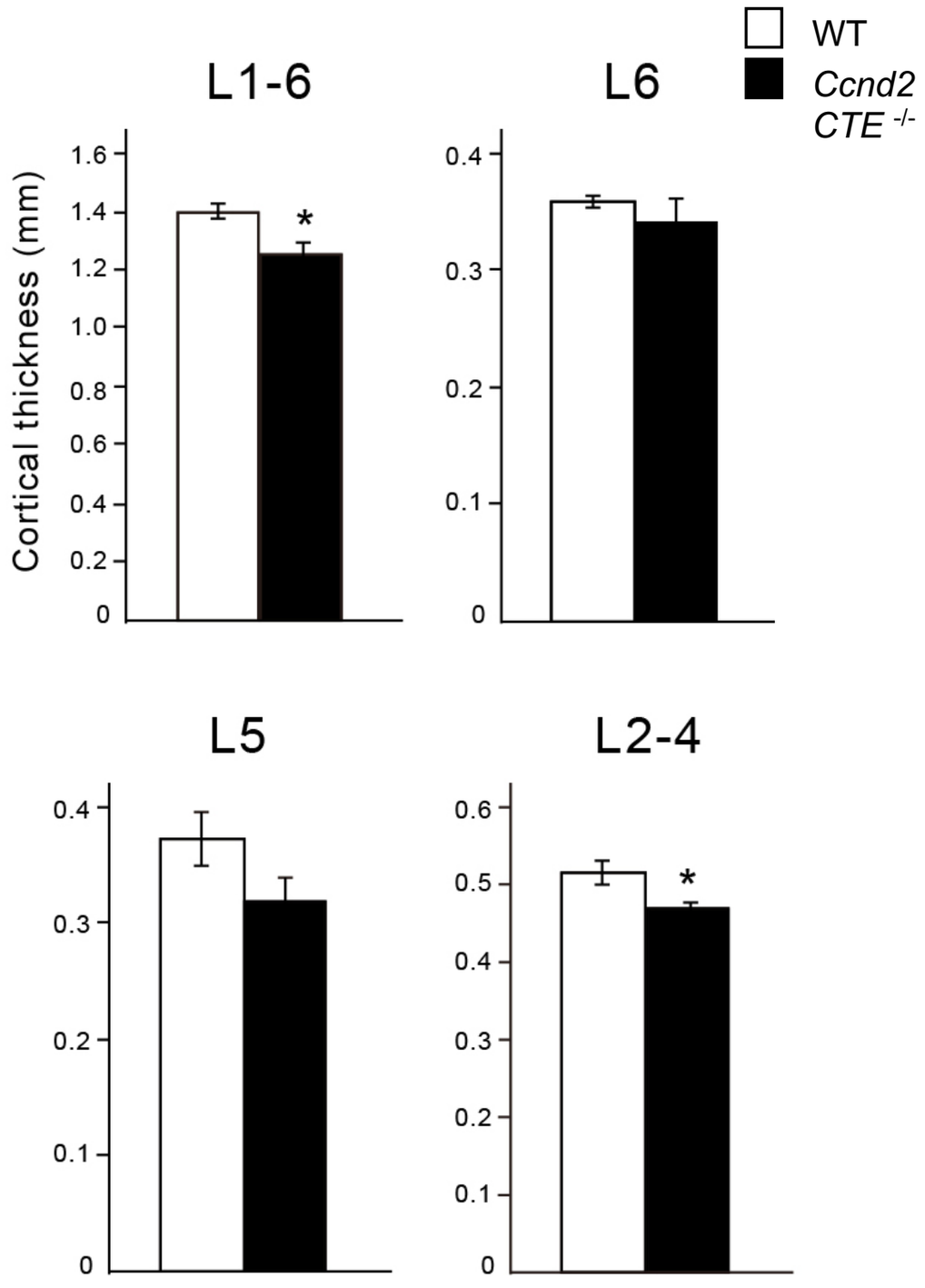
Pilaz et al., 2016

No (or minor?) phenotype in basal endfeet

Kikkawa, unpublished

Impaired layer formation especially in upper layers



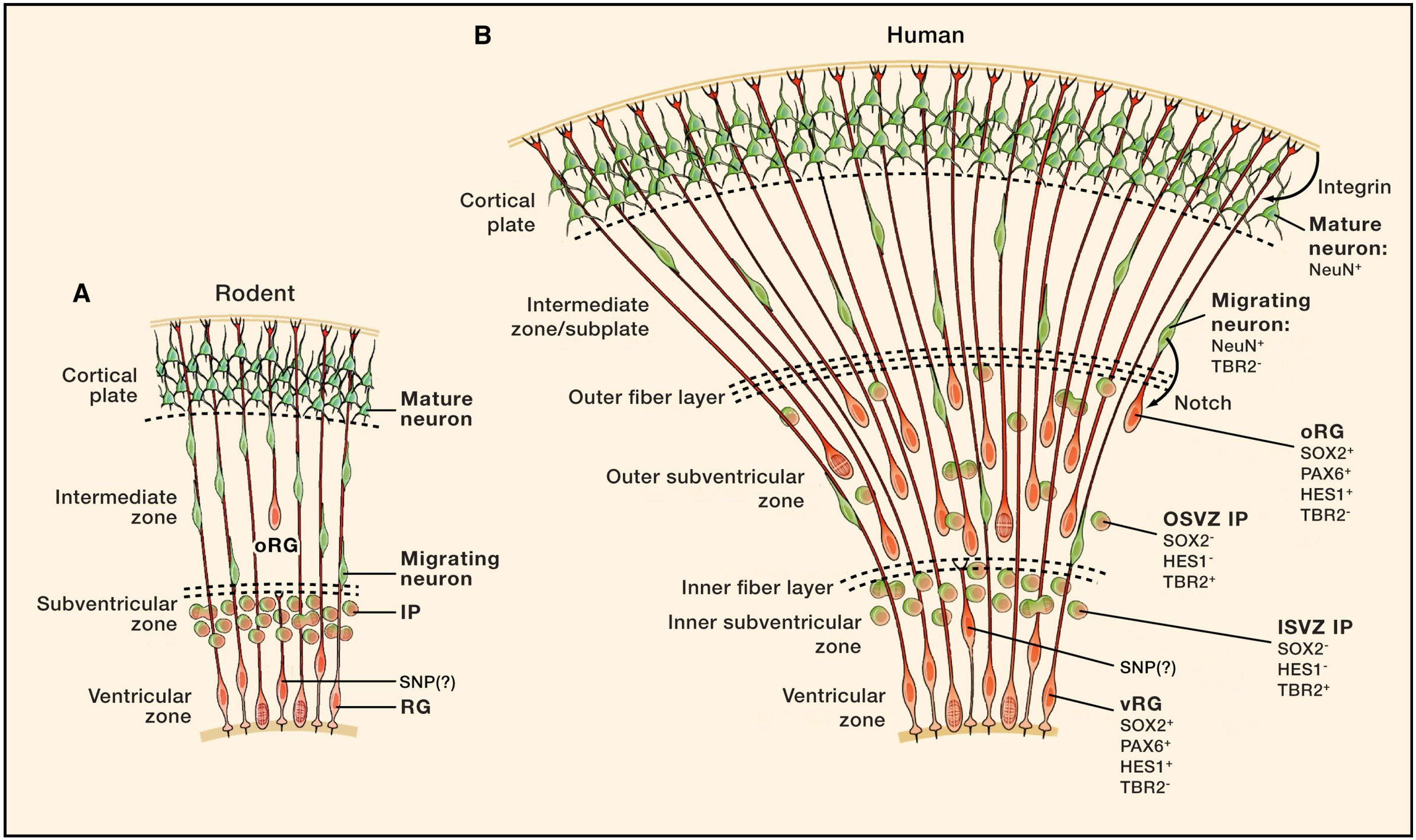


@P10

Kikkawa, unpublished

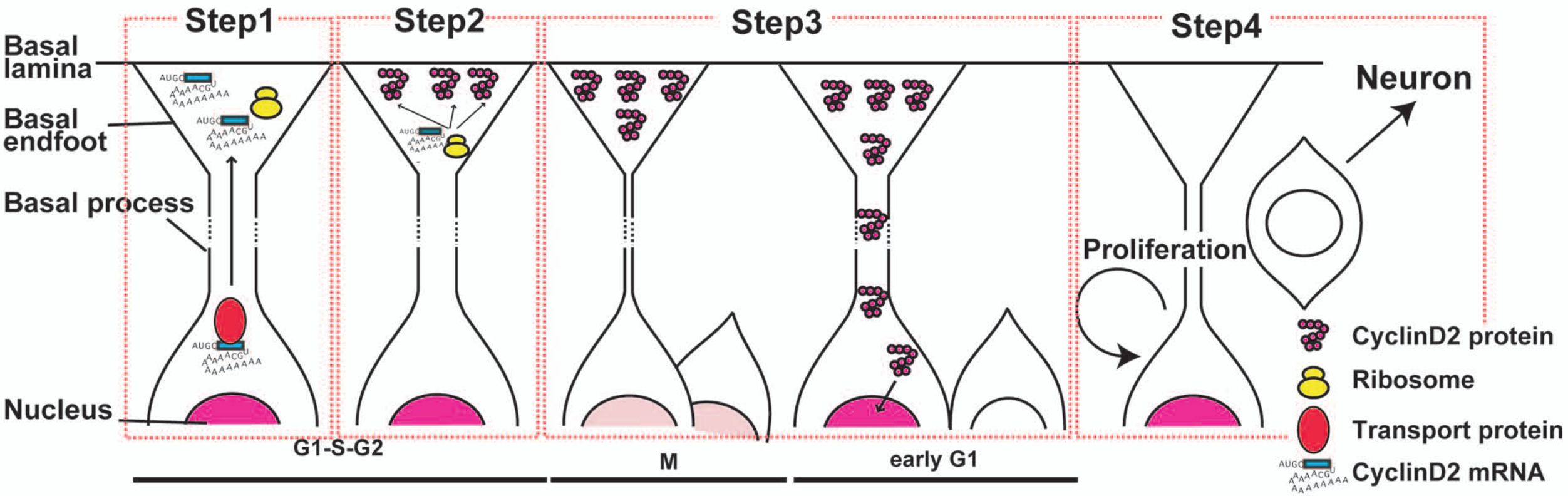
Significance of basal localization of *Cyclin D2*?

Evolutionary implication



Lui et al.: Development and evolution of the human neocortex. Cell, 2011

Basal sequestering of Cyclin D2 affects cell fates



Lengthening of G1 phase?
Allow transcription of longer mRNAs?

Tsunekawa & Osumi, Cell Cycle, 2012

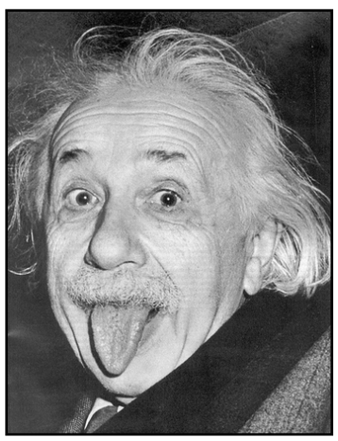
Lengthening of neurogenic period

19 days

0.5 g

21 days

20 g

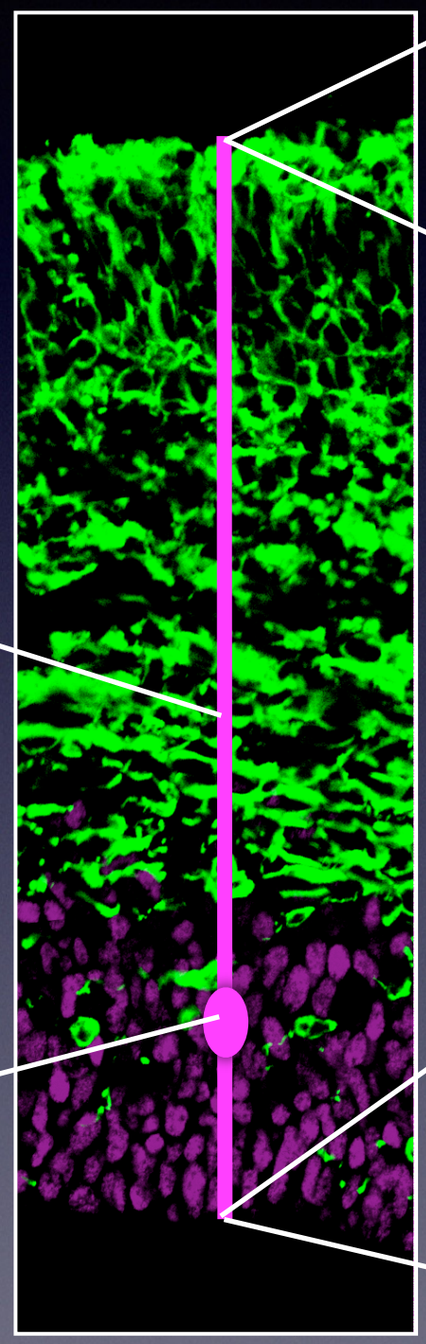


266 days

1500 g

Molecules working together in radial glia

Tuj I: neurons
Pax6: RG



Basal molecules

Secreted molecules
Integrins
Cyclin D2, FMRP

Maintenance of progenitor cells

Radial glial molecules

Fabp7/BLBP
LewisX/CD15
Notch signals

Nuclear molecules

TFs incl. Pax6, Ngn2, Dmrta1
Polycombs
BAF complex

Apical molecules

δ-catenin
Polarity proteins
Centrosomal proteins

My questions
(For your report as well)

- Why more boys than girls in autism?
- Why boy:girl ratio is 1.05:1.00?

Choose one of the above two questions